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SYMPOSIUM ON ARTHRITIS—Continued

A MODERN CONCEPTION OF ARTHRITIS

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ARTHRITIS, long one of the mysteries of medicine, is beginning to yield some of its secrets to modern investigators. The present-day student of this disease makes a primary and fundamental distinction between arthritis due to infection and arthritis dependent on other etiologic factors. Nearly all pathogenic bacteria can, under proper conditions, invade the joint and excite inflammation in it. This is particularly true of the common pathogens of the oral cavity. The bacteria most prevalent in mouth secretions are the staphylococcus, Streptococcus hemolyticus, Streptococcus anhemolyticus, Streptococcus viridans, Pneumococcus, and Bacillus influenzae. All of these bacteria, including the Pfeiffer bacillus, can excite an arthritis. Strangely enough, the Streptococcus viridans, which is the commonest of the mouth inhabitants and the organism most frequently found in tonsils and root abscesses, is the one pathogen which some investigators are most loath to admit as an exciting agent of arthritis. Yet a priori it should be the most frequent excitant of the disease.

Infection is responsible for two-thirds to three-fourths of all cases of arthritis, but there remains a large group of cases which are apparently noninfectious in origin. By far the most prevalent in the noninfectious group is the so-called hypertrophic or degenerative arthritis. All the pathologic and bacteriologic evidence indicates that hypertrophic arthritis is not referable to bacteria, but to the phenomena which accompany senescence.

ACUTE ARTHRITIS

Acute arthritis is usually a complication secondary to bacteriemia. Why is it, however, that many patients with bacteriemia escape arthritis, while others contract the disease? Two factors probably come into play: first, trauma; and second, hypersensitiveness of the joint tissue. It is a well-known fact that an injured joint is prone to infection, constituting by reason of the injury, a

point of lowered resistance. But modern studies, particularly in the domain of rheumatic fever, indicate that bacterial allergy is also instrumental in some cases. Even in rheumatic fever, a disease which is so frequently associated with swollen joints, cases are often seen, especially in children, where the joint involvement is insignificant, the disease manifesting itself in the heart, pericardium, pleura, or brain.

In recent studies conducted in the laboratories of Bellevue Hospital,[1] streptococci usually of the green type have been recovered in a high percentage of cases from both the blood and the joints of patients with rheumatic fever. From this we infer that though bacterial allergy may play an important part in sensitizing the joint tissue, the actual development of rheumatic arthritis in the joint is an infectious process, due primarily to the presence of streptococci in the joint tissue. In other words, the pathogenesis of rheumatic fever differs in no essential respect from that of gonococcal arthritis. In both diseases the sequence of events is:

1. Focal infection
2. Bacteriemia
3. Localization of bacteria in joint; arthritis

CHRONIC INFECTIOUS ARTHRITIS

Investigators of rheumatic conditions have long been impressed with the close similarity between rheumatic fever and chronic infectious arthritis. Both tend to occur in young people, though rheumatic fever is more common in children, and infectious arthritis in young adults. Both diseases appear to be related to foci of infection. Both are characterized by swollen, painful joints. Both may present all the appearance of an acute infection in the early stages, so much so that it is often impossible to differentiate them clinically; both may go on to a chronic form, and about 5 per cent of patients with rheumatic fever progress into a form of chronic arthritis indistinguishable from rheumatoid arthritis. Both diseases may at times involve the muscles and tendons as well as the joints, and both diseases are sometimes complicated by subcutaneous nodules.

A final and quite important point of similarity between rheumatic fever and infectious arthritis has been brought out by the studies in our laboratory (Cecil, Nicholls, and Stainsby[2]). We have found that in chronic infectious arthritis, as well as in rheumatic fever, cultures from the blood and joints will yield streptococci in a high percentage of cases. With rare exceptions the streptococci recovered from arthritic patients differ culturally and biologically from streptococci isolated from patients with rheumatic fever. In the former disease an intermediary type of streptococcus, possessing both hemolytic and green-producing properties, is usually found. In rheumatic fever green streptococci are isolated in the great majority of cases, though occasionally an indifferent streptococcus, of the type described by Small[3] and by Birkhaug,[4] is recovered. Recent studies on the agglutinations are bringing out some interesting facts. Patients with typical chronic infectious arthritis show high agglutinins for the typical arthritic strains in 94 per cent of cases. In rheumatic fever the agglutination reactions are not so strong, but nevertheless are quite definite.

The green streptococci recovered from rheumatic fever patients appear to fall into definite biologic groups analogous to the pneumococcus groups.

The life history of rheumatoid arthritis is similar in all respects to that of rheumatic fever in presenting the same chain of events, namely, focal infection, bacteriemia, and metastatic infection of the joints. In addition to the joint lesions, bacteria sometimes localize in the muscle or tendon sheaths and occasionally in the subcutaneous tissue, with the production of subcutaneous nodules. Complications, such as pleurisy and pericarditis, are not so common in infectious arthritis as in rheumatic fever, though they do occur. McCrae[5] has reported a series of cases of rheumatoid arthritis manifesting pleural or pericardial symptoms. If the streptococcal theory is correct, it is difficult to explain why endocarditis and Aschoff bodies occur with such high frequency in rheumatic fever, whereas in infectious arthritis these lesions are practically never seen. This difference can hardly be dependent on the age of the patient, as children with rheumatoid arthritis (Still's disease) rarely show valvular lesions. The difference must therefore depend upon something in the streptococci themselves.

In order to control the cultures on patients with rheumatic fever and infectious arthritis, blood and joint cultures have been made on normal individuals and patients with conditions other than rheumatism or arthritis. We have never succeeded in recovering a streptococcus from the blood or the joint of a perfectly healthy individual. In four or five instances green streptococci have been isolated from blood cultures of patients with some acute respiratory infection or with some chronic focus of infection such as pansinusitis or chronic tonsillitis. Such findings do not appear to us to militate against acceptance of the streptococcus as a cause of rheumatism and arthritis. It is a well-known fact that both of these diseases usually develop after some acute respiratory infection or in patients who harbor some chronic focus of infection about the throat, sinuses, or teeth. It is not surprising, therefore, that streptococci should occasionally be encountered in the blood streams of patients with these infections.

ANIMAL EXPERIMENTS

Final proof that the streptococcus causes rheumatic fever and infectious arthritis will depend upon the success with which these diseases are reproduced by the streptococci in animals. The animal which has been employed almost exclusively up to the present time is the rabbit. Poynton and Paine,[6] Rosenow,[7] Clawson,[8] and others have reproduced lesions in rabbits with the streptococci recovered from patients with rheumatic fever, and they claim that lesions so produced are practically identical with those which occur in man. There has been some disagreement on this point, however, and pathologists have some difficulty in deciding just what an Aschoff body is. Reproduction of chronic infectious arthritis in rabbits has been a little more successful. Numerous workers, including Rosenow,[7] Haden,[9] Burbank[10] and ourselves, have produced in rabbits chronic joint lesions which bear every resemblance to the human lesions. In our own studies some of the rabbits have developed true deformities and sections taken from the joints are indistinguishable under the microscope from sections taken from the human arthritic joint. Furthermore, cultures

from the blood and joints of the arthritic rabbit usually yield a streptococcus which is culturally and biologically identical with the strain injected.

The recovery of streptococci from a high percentage of patients with rheumatic fever and infectious arthritis, and the reproduction with these streptococci of lesions in rabbits so similar to those in man, make it difficult to resist the conclusion that both rheumatic fever and infectious arthritis are streptococcal infections. The proof is not yet final, but certainly a great deal of evidence has accumulated to support the streptococcal theory.

HYPERTROPHIC ARTHRITIS

As already indicated, hypertrophic arthritis does not present the picture of an infectious disease. Clinically the patients are without the fever, the leucocytosis and the secondary anemia which those with rheumatic fever or infectious arthritis so frequently present. The patient with hypertrophic arthritis is nearly always middle-aged or elderly, and one gets the impression that the joint lesions are simply another phase of senescence.

The pathologic changes in the hypertrophic joint are not those which characterize infection. In infectious arthritis granulation tissue spreads over the articular surfaces and may eventually fuse them together. In hypertrophic arthritis there is no granulation tissue or other evidence of an inflammatory reaction. The cartilage is worn down and fibrillated and the underlying bone is increased in density. Around the margins of the joint the bone is hypertrophied and small bony spurs grow out. Fusion of the articular surfaces does not occur.

The bacteriologic and serologic findings in hypertrophic arthritis give no evidence of an infectious process. In our experience cultures from the blood and joint have been sterile without any exception, and agglutination tests carried out with the patient's blood have never given positive reactions with any of the streptococcal strains. Studies conducted by Pemberton[11] and more recently by Hench[12] indicate that hypertrophic arthritis results from inadequate blood supply, the latter in turn being due to an endarteritis of the small vessels. Improper nutrition of the joint results in a lowering of its resistance to ordinary wear and tear, and when the strain on the joint is excessive, such as exists in the knees of an overweight patient or in the shoulders, fingers and back of certain laborers, hypertrophic arthritis develops. It appears, therefore, that endarteritis is a predisposing cause and trauma the exciting cause of hypertrophic arthritis.

SUMMARY

So far, this paper has been confined largely to a discussion of the exciting agents of arthritis. Before closing, perhaps something should be said about the various predisposing influences which are at work in these diseases. In rheumatic fever the most important predisposing factor is environment. Rheumatic fever is a rare disease among the well-to-do. It is extremely common among the children of the poor. This increase of susceptibility in the poor is probably a combination of improper diet and exposure to cold. The well-to-do are better fed and better clothed and escape infection. Probably another pre-

disposing factor is exposure to a carrier of the rheumatic fever virus. St. Lawrence[13] has pointed out the prevalence of rheumatic fever in two or more children of the same family. This may be heredity, but contagion may also be an important factor.

In both rheumatic fever and infectious arthritis, focal infection is of vital significance. Statistics show that rheumatic fever cannot be prevented by the removal of all foci of infection, but the incidence is considerably reduced.

Other factors are influential in the etiology of infectious arthritis. Among them, nervous or emotional shock should be stressed. It is surprising what a large percentage of these patients give a history of overwork or some emotional disturbance just prior to the onset of arthritis. Other factors, such as trauma and exposure to cold and dampness, sometimes provoke the first attack. I have seen a number of butchers who claim to have contracted arthritis from too many trips to the refrigerator.

In hypertrophic arthritis, overweight and advancing years are the two great predisposing agents. Heredity also plays an important part. Nearly every patient with Heberden's nodes will give a history of a mother or father who was afflicted with the same condition.

This discussion has been nothing more than a cursory review of a complex subject, but perhaps enough has been said to indicate that some of the mysteries of arthritis are on the way to solution, and that with a few more years' intensive research along bacteriologic and physiologic lines, the medical profession will have a fairly concise idea as to the true nature of rheumatism and arthritis.

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CLINICAL OBSERVATIONS IN CHRONIC ARTHRITIS

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THIS review of chronic arthritis is based on seventeen years' observation of patients suffering with joint disease. Certain clinical aspects of these patients have impressed themselves as constantly present and of increasing significance. Since we do not yet know with certainty any one precipitating etiologic factor in the production of arthritis, all data are of importance.

It is generally accepted from a pathologic standpoint that there are two widely divergent types of nontuberculous joint disease, the atrophic and the hypertrophic arthritis. The first is a proliferative reaction[1] about the joint, with general bone atrophy, and the second a degenerative disease of the bony structures, with secondary soft tissue changes. Many place the infectious arthritis in the same group with the atrophic. There are, however, numerous clinical factors in the atrophic picture which are not explained by the bacterial theory alone. Having had the opportunity to study cases over years rather than months, certain differences stand out with increasing clearness as the years go by. For these reasons,[2] the three types of arthritis are used as a means of accurate observation and recording of data.

It has been our experience that most cases of infectious arthritis,[3] even when the disease is severe and overwhelming, do not progress, even in years, into a typical atrophic case, and have very few of the characteristic signs of the latter disease. The only point of resemblance may be the joint manifestations. The constitutional signs and symptoms are not the same. For example, ankylosis occurs in both infectious and atrophic arthritis, but general bone atrophy does not follow in the infectious type, even after years of ill health and invalidism. It does from the first in the atrophic.

There are cases of arthritis undoubtedly due to bacterial infection, where some focus of infection either starts a blood infection and locates in the joint, or makes the joint hypersensitive to its toxins; and therefore an allergic joint is produced. Those foci are in tonsils, teeth, sinuses, intestines, and urinary tract. These cases respond to removal of the infected focus (if it is removed early), and the joints have not become too sensitive to the foreign poisons. They usually are better for the removal of the source of toxemia, and are frequently still further improved by careful use of vaccines. Foci of infection are better removed whenever possible, if by so doing the operation in itself is not more than the patient can stand in his depleted, oversensitive condition. Otherwise he has a better chance to recover in the presence of the focus by general supportive treatment until his immunity, or resistance, has been brought up to a point where removal is safe.

An example of this is a woman who came to the hospital three years ago with a general arthritis, from which she had been incapacitated for a year

and a half. The x-ray study showed no bone atrophy. Clinically, there was little muscle atrophy; a few joints were very nearly destroyed, with thin cartilage, much soft tissue proliferation, and considerable loss of weight. The laboratory study was as follows:

Hemoglobin, 70 per cent; R.B.C., 4,500,000; W.B.C., 16,200. Smear: polymorphonuclears, 50; lymphocytes, 30; large mononuclear cells, 6; eosinophiles, 4; tr., 2.

Galactose Tolerance: 30 gm. ++, 20 gm. perceptible trace, 15 gm. +, 10 gm. light trace, 7 gm. 0.

Blood Chemistry: Sugar, 87-133-138-128; Nonprotein Nitrogen, 35.1; Ca., 11.2; Ph., 11.6.

Basal metabolism, -16, -23, -26. Vital capacity, 2600. On discharge metabolism still -20.

The tonsils were badly infected. Because of her general condition they were not removed at first. She was put to bed, given an ample, well-balanced diet, slightly low in carbohydrates. She had hydrotherapy, massage, and corrective body exercises to improve her posture. She was built up gradually[4] until her joint symptoms of pain, heat, and tenderness had subsided. After four months she was up and about with no active arthritis. She had developed her own resistance. Then her tonsils were removed, and she has had no recurrence of symptoms, objectively or subjectively, since. She has gone back to a normal, unrestricted life. Some joints are still damaged, but are usable and increasingly so. This woman, with a demonstrable focus, depletion, and crippling after a year and a half of active arthritis, showed no tendency to the bone changes constantly present in the atrophic patient.

Infectious arthritis does not have any special age, sex, or type proclivities. It is not a respecter of persons, which cannot be said of either the atrophic or hypertrophic arthritis.

The patient with hypertrophic arthritis never has much trouble from his joints[3] until late in life, and then only when he acutely injures some joint, or when the degenerative changes have reached a point where motion becomes painful and restricted. The degree of joint change seems to depend principally on the amount of daily trauma the joint receives, and is usually found chiefly in the large working joints, such as the low back, hips, knees, and cervical spine. Other joints are affected, but it is usually the weight-bearing ones which receive daily strain, often legitimate but quite frequently from unnecessary postural misuse.

It puts in its appearance late in life, and the degenerative changes are probably largely due to trauma and the inevitable physiologic changes due to advancing years. It is rarely found except in the heavy[5] type of person, and is twice as common in men as in women. This type of arthritis is primarily an orthopedic problem, and is not difficult if the traumatic idea is remembered, unless, of course, the degeneration has so changed the joint that all motion is painful. The principle of treatment is to stop the daily injury by rebalancing the body after the joints have been rested. This is a question of postural correction and changing the weight-bearing of the joints from their strained angles, with back supports, plates, elastic knee supports, and especially training.

Much can be done to make the effects of age less apparent by endocrines,[6] diet, and increased elimination, much as one does for the arteriosclerotic, as many of these cases show arterial changes as well.

The most interesting and difficult cases to treat are those with atrophic arthritis,[7] as they present a complicated physiologic condition. Atrophic arthritis has a distinct hereditary tendency. It is three times as common in woman as in men, and is a disease of early middle life. But almost invariably it appears in the slender, light-boned woman, the congenital visceroptotic type. It is almost never found in the heavy-boned people. These facts have made the controversy between infection and constitutional tendencies an ever-present one. Clinically, the general bone atrophy, the exaggerated muscle atrophy, and the extreme lack of tone, occur early in the disease. There is much data which suggest a constitutional background for the disease. Just which one of many apparent causes precipitates the final break in compensation is not yet certain, but such things as exhaustion, chill, infection, pregnancy, nervous shock, the results of postural defects, all seem to be causes in different cases.

The outstanding clinical facts in these cases are their vasomotor instability, their sympathetic delicacy, and the depletion of their metabolic vitality, as manifested by subnormal body temperature, their abnormally cold extremities, often 20° below body temperature, their low systolic blood pressure, often below 100°, and a low pulse pressure. In a series of 300 cases of arthritis,[6, 8, 14] the basal metabolic rate was below −10 in 60 per cent, and below 0 in 83 per cent. There is usually a chronic, secondary anemia. X-ray studies of the intestines reveal an atonic large bowel with diminished haustral markings, suggesting a low grade colitis.

The atrophic arthritic is very unstable in his superficial circulation with rapid vasomotor changes, manifested by cold, blue hands and feet,[5, 7, 9] and mottling of the skin. He is, therefore, susceptible to cold, changes in weather; and barometric changes often cause acute suffering.

It is interesting to note that these symptoms are frequently present in varying degrees long before the joints are noticed, and are exaggerated as time goes on and the joint symptoms begin. They are warnings of disturbances which precede atrophic arthritis, which is only waiting for the chance cause. Millard Smith recently has suggested that this is part of the disease[10] (arthritis without joint involvement). We feel that these disturbances are forerunners of the inevitable atrophic changes unless they can be corrected.

In a recent series of papers, Kuhns and I have published our convictions[11, 12, 13] that the deformities of arthritis are largely unnecessary, except in exceptionally severe cases. The joint damage is decreased, the resulting deformity, and the acuteness of the arthritis itself are controllable by means of plaster splints, used for intervals, and recurring rest for the joints in the best functional positions. It has been found that early use of rest, protection with supervised voluntary exercise periods, gives the quickest and best results as far as the joints are concerned. It has been quite encouraging to see the surprising improvement of the joints by anticipating the usual deformities.

In reviewing the atrophic cases, it seems evident that by anticipating the arthritis in the slender, unstable, visceroptotic, the arthritis itself can be best

controlled. Having followed many young women with such symptoms, and seen the marked improvement under systematic, continued building up, with rest, corrective exercises and high vitamin diet, I believe that all these potential arthritics should be recognized and built up to robust health as far as possible early, before they have arthritis, when they come for general examination. The potential weakness common to the patient with atrophic arthritis can be corrected gradually and the arthritis in many cases prevented.

The method of treatment can be based on the following facts: That out of 37 cases of atrophic arthritis, 36 were in the D posture class,[14] using the Harvard standard. They are all congenital ptotics, because of their anatomic type.[9] Poor posture and visceroptosis together result in low vitality and diminished health.[15] Our first attack is to correct the posture and thus give the viscera a chance to do more of their work. Second, after thus securing better nutritional conditions, feed the patient the freshest of fruits, vegetables, milk, eggs, whole grains, and all kinds of mineral, vitamin-rich foods, which are alkaline forming and not acid, as these people[5] are extraordinarily acid in their sweat and saliva, and remain so for long periods. Third, complete rest with exercise in bed until they can continue the exercise up and about. Rest is essential. Fourth, sunlight, fresh air, and outdoor exercise if possible. Fifth, regulation of the home activities to secure rest, leisure, relief from nervous strain and worry. Fatigue is probably the most dangerous factor in relapses, as this means neglect of the essentials for health—posture, rest, and sleep. Lowered vitality is followed by an increase in the previously noted symptoms.

No matter what the precipitating cause of the joint involvement is, no matter what the final cause of the atrophic arthritis is found to be, bacteria (Cecil,[16] Burbank,[17] Crowe,[18] etc.), or circulatory (Pemberton,[19] Dowthwaite[20]), or intestinal (Fletcher[21, 22]), this poor physical condition and lack of resistance and instability allow these final factors to become active in the production of the joint changes. Many cases of atrophic arthritis show bone atrophy and joint destruction without subjective joint symptoms. Unless, therefore, something is permanently done to restore this inherent lack of vitality, to restore the circulatory stability, and to put the patient on a higher plane of health, the removal of a focus, the use of a vaccine, of rest, and dieting can be of temporary benefit only. The underlying condition remains as it always has been from childhood up. The goal to be worked for is permanent restoration, if possible, of metabolic stability, so that the environment may be met with some degree of assurance. Oftentimes the atrophic's equilibrium is so poor he cannot even cope successfully with any foreign proteid, vaccine, or endocrine stimulation.[6]

If we are to be permanently successful in the treatment of arthritis of this type, we would do well to look at it from a broad point of view, the same as we do with tuberculosis.

In tuberculosis, an exposed child is taken in hand at once and treated as a potential tuberculous patient until he is well and resistant. Time and care are expected in treating tuberculosis. Atrophic arthritis must be attacked in the same way. Recognize the potential atrophic with the hereditary possibilities, the type of anatomy, the vasomotor instability with the cold, clammy

hands, the chronic fatigue, the lack of vitality, and treat him before any serious damage has been done. In this way it has been possible to prevent at least a few more cripples of the atrophic type. Even if we find a final precipitating cause of atrophic arthritis, we have still to deal with the fundamental physical condition which is back of the ill health of the atrophic patient.

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THE SYNOVIAL FLUID IN HEALTH AND DISEASE WITH SPECIAL REFERENCE TO ARTHRITIS

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THE purpose of this paper is to collect, classify and evaluate, the available data on synovial fluid in order to ascertain, first, whether the known properties of joint exudates can be utilized for clinical purposes, and second, whether further studies on fluid of joints are likely to be of value, and if so, in what direction such investigations should proceed. One is now able, by a study of the physical, chemical, serologic and biologic characteristics of spinal fluid to acquire valuable data for diagnosis, prognosis and treatment of diseases of the central nervous system. The synovial fluid, on the other hand, has been neglected both by the internist and by the surgeon. Many studies on certain special phases of this problem have been undertaken, but no concerted effort has been recorded to carry out complete investigations of the synovial fluid. This is surprising when it is realized that pathologic joint exudate is one of the most easily available body fluids, that it can often be obtained in large amounts and that its withdrawal requires no expert technic, causes little discomfort, and entails practically no risk to the patient provided that strict aseptic precautions are maintained.

From a detailed review of the literature on synovial fluid it was learned that much of the data concerning its physical, chemical and biologic properties has been recorded in numerical values. Because of this it seemed advisable, for the sake of brevity and of convenience in comparison, to tabulate the various findings. Tables I and II list the physical and chemical characteristics together with dates, names of investigators, numbers of cases and diagnoses. Tables III, IV, V and VI list the biologic data, including Wassermann reactions, results of animal inoculation and of culture, together with histologic findings. Table VII is a composite of the other tables.

For information concerning the formation of synovial fluid and of the synovial membrane and their relations to neighboring structures, the reader is referred to the papers of Key,[1] Mayeda[2] and of Franceschini.[3] The cavity which is destined to contain synovial fluid is formed relatively late in embryonic life by a splitting of tissues which form clefts lined by mesenchymal connective tissue cells. These lining cells have been referred to in the literature as endothelial elements, but the evidence is in favor of their being really connective tissue cells rather than endothelium. Forkner, Shands and Poston[4] have suggested that they be called "mesothelial cells."

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TABLE I

PHYSICAL AND CHEMICAL PROPERTIES OF HUMAN SYNOVIAL FLUID. A. NORMAL, GENERAL EDEMA, VARIOUS DISEASES AT AUTOPSY, NONSPECIFIC EFFUSIONS, ACUTE SYNOVITIS, BURSITIS, SEPTIC ARTHRITIS, GONORRHEAL ARTHRITIS, SYPHILITIC SYNOVITIS, AND CHARCOT JOINTS

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	SPECIFIC GRAVITY	VISCOSITY 20° C.	PRESSURE	WATER	SOLIDS	P_H	TOTAL PROTEIN	TOTAL NITROGEN	ALBUMIN	GLOBULIN	ALBUMIN GLOBULIN	SUGAR	SODIUM CHLORIDE	CHLORIDE	N. P. N.	MUCIN	ICTERIC INDEX	GENERAL REMARKS
							MM. Hg.	PER CENT			PER CENT				RATIO	MILLIGRAMS PER 100 C.C.				PER CENT		
Normal	?	Mayeda	2	1919	1.040																	
Normal	?	Fisher	8	1923					4.41		1.6									1.95		Autopsy material
										8.2												
Normal	?	Seeliger	9	1926						8.4												
						3.9																Autopsy
Various Diseases (No Arthritis)	30	Schneider	10	1925		1490																material
General Edema	1	Boots and Cullen	11	1922						7.34												
General Edema	1	Cajori and Pemberton	12	1928		4.71					1.39		1.03	.025	41.0					0.42		
					1.008			94.49	1.20	weak			0.45									
General Edema	25	Horiye	13	1924	1.018			98.80	5.51	alk.			3.90									
?							68															
Serous Effusion	2	Ranke	14	1875			272															
?							204															
Bloody Effusion	?	Ranke	14	1875			2720															
?										7.21												
Hydrops Non-specific	5	Habler	15	1928						7.58												
?	16	Fremont-Smith and Dailey	16	1926				93.7			3.63					72		354	19			
Effusion								96.1			6.33					119		408	33			

TABLE I—CONT'D

? Effusion	9	Cajori and Pemberton	12	1928														573 623		22 29				
? Effusion	11	Cajori and Pemberton	12	1928		2.91 4.79					3.54 6.02		2.26 3.72	0.31 2.45	1.2 8.8						0.41 0.65			
? Effusion	1	Cajori and Pemberton	12	1928						6.5 6.6						8 10								
Acute Synovitis	1	Hammarsten	17	1882	1.017				5.28		3.92										0.27			
Synovitis	7	Kling	18	1930																		2.8 5.3		
Bursitis	2	Kling	18	1930																		3.5 3.8		
Septic Arthritis	?	Ranke	14	1875			272 748																	
Septic Arthritis	2	Boots and Cullen	11	1922						6.19 6.69														
Septic Arthritis	3	Allison et al	7	1926							3.56 6.92							556 577		23 27				
Septic Arthritis	4	Allison et al	7	1926												19 43								
Septic Arthritis	4	Habler	15	1928						6.58 7.24														
Septic Arthritis	5	Rostock	19	1929			150 420																	
Septic Arthritis	1	Kling	18	1930																		5.2		
Gonorrheal Arthritis	1	Habler	15	1928						6.97														
Gonorrheal Arthritis	1	Kling	18	1930																		4.7		
Syphilitic Synovitis	1	Kling	18	1930																		3.9 4.0		
Charcot Joint	1	Kling	18	1930																				

TABLE II

PHYSICAL AND CHEMICAL PROPERTIES OF HUMAN SYNOVIAL FLUID. B. TRAUMATIC EFFUSION, CHRONIC ARTHRITIS, ACUTE RHEUMATIC FEVER, TUBERCULOUS ARTHRITIS, ARTHRITIS OF SERUM DISEASE AND INTERMITTENT HYDRARTHROSIS

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	SPECIFIC GRAVITY	VISCOSITY 20° C.	PRESSURE (MM. FLUID)	WATER (PER CENT)	SOLIDS (PER CENT)	P_H	TOTAL PROTEIN (PER CENT)	TOTAL NITROGEN (PER CENT)	ALBUMIN (PER CENT)	GLOBULIN (PER CENT)	SUGAR (MILLIGRAMS PER 100 C.C.)	SODIUM CHLORIDE (MILLIGRAMS PER 100 C.C.)	N.P.N. (MILLIGRAMS PER 100 C.C.)	MUCIN (PER CENT)	ICTERIC INDEX
Traumatic effusion	11	Habler	15	1928						7.13 7.50									
Traumatic effusion	5	Lasch	30	1928						7.39 7.68									
Traumatic effusion	22	Rostock	19	1929			0 340												
Traumatic effusion (bloody)	34	Rostock	19	1929			0 700												
Traumatic effusion	18	Kling	18	1930															7.40 28.0
Traumatic arthritis	1	Cajori et al.	6	1926		3.3			6.25	7.58	4.18	0.71					40		
Chronic arthritis or traumatic effusion	8	Allison et al.	7	1926							3.64 6.33						19 29		
Chronic arthritis or traumatic effusion	10	Allison et al.	7	1926											58 103	584 674			
Chronic arthritis or traumatic effusion (during anesthesia)	6	Allison et al.	7	1926												592 636	21 34		
Chronic arthritis or traumatic effusion	7	Allison et al.	7	1926											89 116				

TABLE II—CONT'D

Chronic arthritis or traumatic effusion	5	Allison et al.	7	1926							3.70 5.67									
Chronic arthritis	?	Ranke	14	1875			68 395													
Chronic arthritis	1	Hammarsten	17	1882	1.017				5.28		3.92								0.27	
Chronic arthritis	1	Salkowski	31	1893				93.08			5.20						7.72		0.38	
Chronic arthritis	1	Boots and Cullen	11	1922						7.33 7.47										
Chronic arthritis (deformans)	?	Seeliger	9	1926						8.2 8.4										
Chronic arthritis	10	Cajori et al.	6	1926						6.99 7.58	4.40 7.25	0.74 1.16								
Chronic arthritis	14	Cajori et al.	6	1926											73 132					
Chronic arthritis	8	Cajori et al.	6	1926		2.7 16.7			6.03 7.62							409 633	22 43			
Chronic arthritis (deformans)	5	Habler	15	1928						7.01 7.58										
Chronic arthritis	3	Lasch	30	1928						7.64 7.90										
Acute rheumatic fever	8	Boots and Cullen	11	1922						7.27 7.42										
Tuberculous arthritis	2	Allison et al.	7	1926											45 61					
Tuberculous arthritis	1	Habler	15	1928						7.06										
Arthritis of serum disease	1	Boots and Cullen	11	1922						7.33 7.47										
Intermittent hydrarthrosis	1	Boots and Cullen	11	1922						7.37 7.47										

There is considerable discussion and uncertainty concerning the origin of synovial fluid. The following theories, among others, have been advanced: (1) It is the product of physiologic destruction and disintegration of tissues of the joint brought about by movement. (2) It is a transudate from blood or lymph vessels. (3) It is a mixture of transudate and disintegration products. (4) It is a secretion of the synovial lining cells. (5) Certain special cells are present in the so-called synovial membrane for the secretion of mucin or related substances. None of these theories has gained general acceptance.

An opinion is current, which appears to be entirely without scientific support, that synovial fluid is a "dead" fluid and that it really possesses no important functions other than that of lubrication. Some of the earliest chemical studies, on the other hand, as Tables I to VII show, demonstrated that this fluid not only contains a lubricating factor, that is to say, mucin or related substances, but also is rich in proteins, inorganic salts, and sugar. Strangeways[5] in 1920 advanced additional evidence to show that synovial fluid possesses nutritive functions. He examined loose bodies in the joint which were composed of living growing cartilage and bone cells. These tissues had no other source for their nourishment than from synovial fluid. He believed that the primary cause of changes in certain types of arthritis was to be found not in the cartilage or bone, but in changes of the nutritive value of joint fluid. Cajori, Crouter and Pemberton[6] studied synovial fluid extensively from the chemical point of view and concluded, "The adequacy of the synovial fluid for the nutrition of cartilage from the standpoint of carbohydrate and energy-yielding content is clearly indicated."

Allison, Fremont-Smith, Dailey and Kennard[7] found that in noninfected synovial fluids the sugar content was nearly always lower than in the blood plasma, whereas the protein was always lower and the chloride always higher than in the blood plasma.

NORMAL SYNOVIAL FLUID

Physical and Chemical Properties (Table I).—The normal synovial fluid of man is a transparent, highly viscous, almost acellular fluid about which very little reliable information is recorded. Because of the small amount of fluid contained within the capsule of normal joints, and because of the lack of interest in the synovial fluid generally, research in this field has been limited. The specific gravity is reported as 1.040, total solids as 4.41 per cent, total protein 1.6 per cent, mucin content 1.95 per cent and P_H as 8.2 to 8.4. These analyses have not been confirmed and they are, therefore, purely provisional values. Judging from the extensive work on the P_H of pathologic synovial fluid it seems that the P_H values of normal synovial fluid as recorded by Seeliger[9] (Table I) are too high. It is much more probable that the P_H approximates that of the circulating blood.

Biologic Properties (Table III).—There are conflicting results concerning the cytology of normal synovial fluid. The total white cell count as recorded by Labor and von Balogh[21] is from 10 to 20 cells per cubic millimeter. They

found no red blood corpuscles. Hammar,[20] working much earlier and with crude methods, found red corpuscles in the fluid of normal joints at autopsy. A recent study by Key[22] indicates that there are from 80 to 375 white cells and about an equal number of red blood cells per cubic millimeter in the normal synovial fluid of rabbits and children. These results were obtained from fluid recovered at operation, presumably under an anesthetic, and it seems entirely probable that the unavoidable trauma or congestion of vessels under such conditions may lead to an increased cellular content. Pending a confirmation of the above findings it may be assumed, tentatively, that normal synovial fluid contains ±50 white cells per cubic millimeter.

As regards the differential cell count we have only the unconfirmed results of Key[22] which are recorded in Table III. He divides the cells into six general types, synovial lining cells, primitive cells, polymorphonuclear leucocytes, indeterminate phagocytic cells, clasmatocytes and monocytes. He did not find lymphocytes. On the other hand, numerous investigators studying the cells of various pathologic fluids have often noted that lymphocytes are present. No other investigator has recorded the finding of so-called "primitive" or undifferentiated cells in synovial fluid. In the discussion of the types of cells encountered, Key[22] makes the following statement: "Since it has been shown by Cunningham, Sabin, and Doan that the primitive cells develop into monocytes, all clasmatocytes, monocytes, indeterminate mononuclear phagocytes and primitive cells may be grouped together as the macrophage series." This is indeed confusing and would appear to be an unjustified assumption. Cunningham, Sabin and Doan[28] believe that not only monocytes, but all of the white blood cells are derived from "primitive" undifferentiated cells by a process of orderly differentiation. Moreover, the above authors do not group together primitive cells, monocytes, and clasmatocytes as cells of the macrophage series. The terms "macrophage" and "clasmatocyte" are quite synonymous and imply that these cells are phagocytic for large and small particles or for cellular débris. The primitive cell of Cunningham, Sabin and Doan,[28] on the contrary, is undifferentiated and incapable of phagocytosis.

It would seem unnecessary that a new classification be adopted for the cells of synovial fluid. The classification of Key omits lymphocytes and includes primitive cells and indeterminate phagocytes. In these respects it differs from that of all other investigators.

Forkner, Shands and Poston[4] described the living cells of the synovial fluid as they appear when stained, by means of the supravital technic, with neutral red and Janus green. They found in the joint fluid representatives of all the white cells commonly present in normal blood and in addition macrophages and synovial lining cells or mesothelial cells. It is not essential, for cytologic studies, that the supravital technic be used, but it has been well established by numerous investigators that this method provides the best available means for the differentiation of monocytes, lymphocytes, and macrophages. Forkner[29] has recently described in detail the exact methods now

TABLE III

BIOLOGIC PROPERTIES OF HUMAN SYNOVIAL FLUID. A. NORMAL, SIMPLE EFFUSION, NONSPECIFIC HYDROPS, INTERMITTENT HYDRARTHROSIS, TRAUMATIC EFFUSION, TRAUMATIC ARTHRITIS, AND ARTHRITIS OF DYSENTERY

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER	DATE OF OBSERVATION	WASSERMANN		ANIMAL INOCULATION	CULTURE	CYTOLOGY								GENERAL STATEMENTS
				BLOOD	FLUID			TOTAL COUNT		PERCENTAGE						
								R.B.C.	W.B.C.	GRANULOCYTES	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MESOTHELIAL CELLS		
Normal (autopsy)	?	Hammar	1894					+	+		+			+		Also noted presence of threads, fat droplets, degenerating cells, membranes, elastic fibers, and tissue masses
Normal (autopsy)	?	Labor and von Balogh	1919					0	10 20				+	+		
Normal (children)	?	Key	1928					80 375	80 375	0 12		42 84	4 28	0 7		Also noted primitive cells 0-10 per cent, and indeterminate phagocytes 3-29 per cent
General edema (without arthritis)	?	Labor and von Balogh	1919					0	0 20				50	50		
Acute general sepsis (without arthritis)	?	Labor and von Balogh	1919						±400					50		
Nonspecific hydrops	?	Labor and von Balogh	1919						± 40,000							Cell count high during stage of increasing fluid
Nonspecific hydrops	4	Habler	1928				Neg.									

TABLE III—CONTINUED

Intermittent hydrarthrosis	1	Dopter and Tanton	23	1901						+		100					
Intermittent hydrarthrosis	1	Dopter and Tanton	23	1901							50	50					
Intermittent hydrarthrosis	1	Boots and Cullen	11	1922				Neg.									
Intermittent hydrarthrosis	1	Baker	24	1928				B. Melitensis		6,500							Associated with malta fever
Intermittent hydrarthrosis	1	Shands	25	1930				Streptococcus viridans									Associated with multiple infectious arthritis
Intermittent hydrarthrosis	1	Shands	25	1930				Staphylococcus albus (atypical)									Associated with multiple infectious arthritis
Intermittent hydrarthrosis	1	Shands	25	1930				Staphylococcus aureus									No association with infectious arthritis
Traumatic effusion	11	Habler	15	1928				Neg.									
Traumatic arthritis	1	Dopter and Tanton	23	1901					+	+		+					
Traumatic arthritis	8	Julliard	26	1902					+	+	0.5 100	0 33	0 5		0 98		R.B.C. from 7 to 99 per cent W.B.C. from 1 to 93 per cent
Traumatic arthritis	2	Shands	25	1930				Neg.			Predominate						
Traumatic arthritis	1	Shands	25	1930				Streptococcus viridans			Predominate						
Traumatic arthritis	1	Shands	25	1930				Staphylococcus aureus			Predominate						
Arthritis of dysentery	7	Singer	27	1915						+	+	+					
Arthritis of dysentery (acute)	?	Labor and von Balogh	21	1919						2,000 5,000	Predominate	+			2 3		
Arthritis of dysentery (convalescent)	?	Labor and von Balogh	21	1919						750 1,500	+	+			4 5		Lymphocytes may exceed polynuclears

used in Doctor Sabin's laboratory for the application of the supravital technic to the study of blood and tissue cells.

Pending further investigations it may be tentatively accepted that the white cell formula of normal synovial fluid is as follows: Mesothelial cells ±3 per cent, polymorphonuclear leucocytes or granulocytes ±5 per cent, large phagocytic cells or macrophages ±30 per cent, and monocytes ±58 per cent. Whether or not lymphocytes are present is still an open question.

SYNOVIAL FLUID IN CONDITIONS OF GENERALIZED EDEMA WITHOUT ARTHRITIS

Physical and Chemical Characteristics (Table I).—The specific gravity is apparently between 1.008 and 1.018, considerably lower than normal. The viscosity has been recorded in one case as 4.71. The water content ranges from 94.49 to 98.80 per cent, and total solids from 1.20 to 5.51 per cent. The P_H has been determined in only one case and was 7.34. Total protein recorded in one case was 1.39 per cent. The quantity of albumin has a wide variation from 0.45 to 3.90 per cent, and globulin in one case was only 0.025 per cent, giving an albumin-globulin ratio of 41. Mucin in one case measured 0.42 per cent.

Biologic Properties (Table III).—Bacteriologic studies in one case (not included in table) recorded by Boots and Cullen[11] were negative. Labor and von Balogh[21] make the statement, unsupported by protocols, that the total white cell count is either normal or below normal and that macrophages and mesothelial cells are present in about equal numbers. They found no red blood corpuscles.

NONSPECIFIC JOINT EFFUSIONS

Under this heading is included a heterogenous group of cases which are recorded in the literature without definite diagnoses. Most of the cases probably represent one or another type of arthritis. Any conclusions from data of this sort must, therefore, be accepted with reservations.

Physical and Chemical Properties (Table I).—The viscosity in 11 cases has varied from 2.91 to 4.79. Pressure measured in millimeters of water or of synovial fluid in 2 cases of serous effusion was 68 and 272 mm. With bloody effusion the pressure was often much higher, from 204 to 2720 mm. Water content from 93.7 to 96.1 per cent has been recorded in 16 cases. The P_H was on the alkaline side in five cases, from 7.21 to 7.58. In one case in which there was a leucocyte count of over 13,000 cells per cubic millimeter and in which there was a low sugar content (8 to 10 mg. per 100 c.c.) and in which rapid glycolysis was present, the P_H shifted to the acid side, 6.5 to 6.6. Total protein is increased in such cases, ranging from 3.54 to 6.33 per cent. Albumin and globulin are present in concentrations of from 2.26 to 3.72 and from 0.31 to 2.45 per cent respectively. The albumin: globulin ratio varied from 1.2 to 8.8. Sugar in the recorded cases approximated that of the blood, from 72 to 119 mg. per 100 c.c. except in the one case mentioned above in which the

sugar fell to 8 or 10 mg. per 100 c.c. and the lactic acid content rose to 52 mg. per 100 c.c. The chloride concentration ranged from 354 to 408 mg. per 100 c.c. as recorded in 16 cases by Fremont-Smith and Dailey.[16] Sodium chloride varied from 573 to 623 mg. per 100 c.c. in nine cases reported by Cajori and Pemberton.[12] Nonprotein nitrogen measured from 19 to 33 mg. per 100 c.c. in 25 cases. Mucin was decreased and varied from 0.41 to 0.65 per cent.

Some of the chemical constituents of synovial fluid have been determined only in isolated instances and these are not recorded in the tables. For example, Cajori and Pemberton[12] determined the fibrin content in three non-infected synovial fluids and found values ranging from 16 to 50 mg. per 100 c.c. In the fluid of one case of traumatic arthritis Cajori, Crouter and Pemberton[6] found a CO_2 value of 55.2 per cent by volume. The urea nitrogen concentration was determined by Cajori and Pemberton[12] in four non-infected synovial fluids, and it varied from 13 to 18 mg. per 100 c.c. In six similar cases the amino-acid nitrogen varied between 4.7 and 6.8 mg. per 100 c.c.

Biologic Characteristics (Table III).—Cultures of the synovial fluid were negative in 4 cases. It has been stated by Labor and von Balogh[21] that during the stage of increasing fluid in the joint the white cell count may rise to 40,000 per cubic millimeter.

INTERMITTENT HYDRARTHROSIS

Physical and Chemical Characteristics (Table II).—The only record available is a study of the hydrogen-ion concentration in one case recorded by Boots and Cullen.[11] They found a P_H value of from 7.37 to 7.47.

Biologic Properties (Table III).—Culture of the fluid in the above case was negative. Baker[24] recorded one case associated with malta fever in which B. Melitensis was repeatedly grown in pure culture from the joint fluid. In this case the total white cell count of the synovial fluid on one occasion was 6,500 cells per cubic millimeter. Dopter and Tanton[23] record two cases in one of which all the cells present were lymphocytes and in the other, half of the cells were granulocytes and half lymphocytes. Shands[25] has recently cultured three fluids; in one Streptococcus viridans and in the other two, staphylococci were isolated.

TRAUMATIC EFFUSION AND TRAUMATIC ARTHRITIS

Physical and Chemical Characteristics (Table II).—In one case the viscosity is recorded as 3.3. Rostock[19] found the intra-articular pressure in 56 patients to vary from 0 to 700 mm. of fluid. Total solids in one case of traumatic arthritis measured 6.25 per cent. P_H varies from 7.13 to 7.68 and total protein from 3.64 to 6.33 per cent. Total nitrogen in one case measured 0.71 per cent. Allison, Fremont-Smith, Dailey and Kennard[7] reported a series of cases including both traumatic effusion and chronic arthritis in which they found the sugar to be between 58 and 103 mg. per 100 c.c. and sodium chloride between 584 and 674 mg. per 100 c.c. They found also that the chemical constituents of these cases were not materially changed when the patient was

under anesthesia. In six anesthetized patients the nonprotein nitrogen of the synovial fluid varied from 21 to 34 mg. per 100 c.c. The icteric index in 18 cases recorded by Kling[18] varied from 7.4 to 28.0.

Biologic Characteristics (Table III).—The Wassermann reaction in cases of traumatic effusion is uniformly negative unless the patient also has a positive Wassermann in the blood. In such cases, although there is no evidence that the arthritis is syphilitic in origin, the positive reaction may be carried over into the synovial fluid of the blood. Four such cases are recorded by Kling.[32] Habler[15] cultured fluids from 11 cases of traumatic effusion with negative results. There is no record in the literature of either total white cell counts or total red corpuscle counts in the synovial fluid of any case of traumatic effusion or traumatic arthritis. There is one constant finding, however, that red blood corpuscles have been uniformly present, sometimes in large numbers, in some cases constituting 99 or more per cent of the total number of cells present. Apparently the percentage of granulocytes or polymorphonuclear cells may vary from 1 or 2 up to 100 per cent of the white cells. Lymphocytes have been recorded from 2 to 33 per cent. Monocytes in one case constituted 5 per cent. Mesothelial cells have varied from none up to 98 per cent of the colorless cells. Shands[25] reported four cases in which polymorphonuclear cells predominated.

CHRONIC NONSPECIFIC ARTHRITIS

Under this category are included the diseases which have been called chronic infectious arthritis, atrophic arthritis, hypertrophic arthritis, arthritis deformans, rheumatoid arthritis, etc. No attempt will be made here to discuss the classification of arthritis or to subclassify the diseases coming under the general heading of chronic nonspecific arthritis.

Physical and Chemical Properties (Table II).—Ranke[14] found the intra-articular pressure in cases of chronic arthritis to be from 68 to 395 mm. of fluid. The specific gravity in one case has been recorded as 1.017. Viscosity in eight cases measured 2.7 to 16.7. In one case the water content was 93.08 per cent. Total solids have varied from 5.28 to 7.62 per cent, a value lower than 6.0 per cent having been obtained in but one case of nine. The P_H has been studied by six investigators, four of whom found values ranging from 7.0 to 7.58. Lash[30] recorded higher values of 7.64 to 7.90, while Seeliger[9] recorded an even more alkaline reaction of 8.2 to 8.4. Total protein varies between 3.92 and 7.25 per cent, whereas total nitrogen ranges from 0.74 to 1.16 per cent. The sugar content in fourteen cases measured from 73 to 132 mg. per 100 c.c. Salkowski[31] in 1893 found in one case a very high sodium chloride value of 772 mg. per 100 c.c. More recent work on eight cases showed lower values of from 409 to 633 mg. per 100 c.c. The nonprotein nitrogen values vary from 22 to 43 mg. per 100 c.c. The mucin content is given in one case as 0.27 and in another as 0.38 per cent.

The following chemical data are not recorded in the tables because they represent isolated determinations. Salkowski[31] in 1893, in the fluid of a case

of chronic arthritis, found 569 mg. of cholesterin, 17 mg. of lecithin and 282 mg. of fat per 100 c.c. Cajori, Crouter and Pemberton[6] found lactic acid in the fluids of two patients represented by 13 and 28 mg. per 100 c.c. In sixteen cases these observers recorded that the CO_2 content ranged from 43.1 to 68.1 per cent by volume and in three cases calcium varied from 8.3 to 10.7 mg. per 100 c.c. The amount of uric acid in the synovial fluids of seven patients recorded by these workers was from 3.3 to 4.7 mg. per 100 c.c.

Biologic Properties (Table IV).—The table shows the history of the bacteriologic findings in the synovial fluid in this group of diseases. Various kinds of organisms have been isolated. Apparently the green streptococcus, the hemolytic streptococcus, and the gonococcus are the chief offenders. Forkner[45] and Forkner, Shands and Poston[4] have recently reported the finding of gonococci in pure culture on repeated occasions in the synovial fluid and axillary lymph nodes of a case of chronic infectious arthritis. The latter writers in 1928 also reported the isolation in four other cases of green streptococci from both the joints and regional lymph nodes. They pointed out that the presence of the same organism in both the lymph nodes and joints pointed toward these organisms as at least one of the contributing agents in the etiology of their cases. Shands[25] in another series of 42 cases has extended this work and has cultured organisms from 26 of 42 cases (60.9 per cent). The recent work of Cecil, Nichols and Stainsby[44] has given similar results.

There has been very little work on the cytology of joint fluid in chronic nonspecific arthritis. Three cases of syphilis reported by Chesney, Kemp, and Baetjer,[43] having chronic arthritis, presumably of a nonsyphilitic type, had a high percentage of granulocytes in the synovial fluid and the total white cell counts in the fluids of two of them were 1,500 and 2,480 cells per cubic millimeter. Forkner, Shands and Poston[4] studied the cytology of the joint fluid in eight cases, in which bacteria were cultured, and in twenty-two cases in which the synovial fluid was sterile. They found wide variations in both the total and differential counts in each series of cases, but demonstrated that the average white cell count and the percentage of polymorphonuclear cells in the bacteriologically positive fluids was considerably greater than in the sterile joint fluids. These findings have been extended and confirmed by Shands.[25]

ACUTE RHEUMATIC FEVER

Physical and Chemical Properties (Table II).—All that we know on this subject is that the P_H in a series of eight cases was from 7.27 to 7.42.

Biologic Properties (Table V).—Cultures of joint fluid in eight patients with acute rheumatic fever recorded by Boots and Cullen[11] were consistently negative. Labor and von Balogh[21] stated that the white cell count of the synovial fluid was about 7,000 cells per cubic millimeter of which about 3 per cent were mesothelial cells and the remainder were granulocytes and lymphocytes. In 1900 Widal[48] stated that the majority of cells were polymorphonuclears and this was confirmed by Swift.[49]

TABLE IV

BIOLOGIC PROPERTIES OF HUMAN SYNOVIAL FLUID. B. CHRONIC ARTHRITIS

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	WASSERMANN		ANIMAL INOCULATION	CULTURE	CYTOLOGY								GENERAL STATEMENTS
									TOTAL COUNT		PERCENTAGE						
					BLOOD	FLUID			R.B.C.	W.C.	GRANULOCYTES	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MESOTHELIAL CELLS		
Chronic arthritis (rheumatoid)	?	Schüller	33	1893			+	Small bacillus									
Chronic arthritis (infectious)	?	Chauffard and Raymond	34	1896				Negative									Found diplobacilli in scrapings from lymph nodes and in synovial fluid
Chronic arthritis (rehumatoid)	18	Bannatyne et al.	35	1896				Small bacillus									
Chronic arthritis (rheumatoid)	1	von Dungern and Schneider	36	1898							+		+				Chiefly polymorphonuclears
Chronic arthritis	?	Widal and Ravault	37	1900							+						Polynuclears predominate
Chronic arthritis	1	Dopter and Tanton	23	1901							+				+		
Chronic arthritis	1	Juillard	26	1902							87	7	2		4		R.B.C. 48 per cent W.B.C. 52 per cent
Chronic arthritis (infectious)	2	Abadie	38	1902								+	+		+		R.B.C. 60 per cent
Chronic arthritis (rheumatoid)	1	Poynton and Paine	39	1902			+	Diplococcus									
Chronic arthritis	2	Davis	40	1912							+						Small number of polynuclears
Chronic arthritis (deformans)	4	Davis	41	1913				Negative									

TABLE IV—CONT'D

Chronic arthritis (infectious)	5	Billings et al.	42	1922				Green streptococcus									
Chronic arthritis	1	Billings et al.		1922				Hemolytic streptococcus									
Chronic arthritis	1	Billings et al.		1922				Nonhemolytic streptococcus									
Chronic arthritis (nonsyphilitic)	3	Chesney et al.	43	1926	+	+	Neg.	Negative		1,500 2,480	80 89 100	20 11 0					
Chronic arthritis (deformans)	6	Habler	15	1928				Negative									
Chronic arthritis (infectious)	11	Forkner, Shands and Poston	4	1928				Green streptococcus									Unselected cases
Chronic arthritis	2	Forkner, Shands and Poston	4	1928				Gonococcus									
Chronic arthritis (hypertrophic)	1	Forkner, Shands and Poston	4	1928				Staphylococcus aureus									
Chronic arthritis (infectious and hypertrophic)	49	Forkner, Shands and Poston	4	1928				Negative									
Chronic arthritis infectious and hypertrophic	8	Forkner, Shands and Poston	4	1928				Positive	Rare	11,000 ±	61 ±	19 ±	15 ±	3 ±			
Chronic arthritis infectious and hypertrophic	22	Forkner, Shands and Poston	4	1928				Negative	Rare	4,800 ±	48 ±	27 ±	21 ±	3 ±	1 ±		
Chronic arthritis (infectious)	1	Cecil et al.	44	1929				Hemolytic streptococcus									
Chronic arthritis	2	Cecil et al.	44	1929				Negative									Cultures from curettings of joints
Chronic arthritis	1	Cecil et al.	44	1929				Hemolytic streptococcus									Cultures from curettings of joints

TABLE IV—CONT'D

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	WASSERMANN		ANIMAL INOCULATION	CULTURE	CYTOLOGY								GENERAL STATEMENTS
									TOTAL COUNT		PERCENTAGE						
					BLOOD	FLUID			R.B.C.	W.C.	GRANULOCYTES	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MESOTHELIAL CELLS		
Chronic arthritis	1	Cecil et al.	44	1929				Streptococcus viridans									Cultures from curettings of joints
Chronic arthritis	1	Cecil et al.	44	1929				Streptococcus nonhemolyticus									Cultures from curettings of joints
Chronic arthritis	1	Cecil et al.	44	1929				Diphtheroid									Cultures from curettings of joints
Chronic arthritis	1	Boots and Cullen	11	1922				Negative									
Chronic arthritis	14	Shands	25	1930				Streptococcus viridans									The total and differential cell counts in the positive and negative joint fluids were essentially the same as in the cases reported by Forkner, Shands and Poston (4)
Chronic arthritis	2	Shands	25	1930				Streptococcus nonhemolyticus									
Chronic arthritis	1	Shands	25	1930				Streptococcus hemolyticus									
Chronic arthritis	4	Shands	25	1930				Staphylococcus aureus									
Chronic arthritis	4	Shands	25	1930				Staphylococcus albus									
Chronic arthritis	1	Shands	25	1930				Hemolytic staphylococcus aureus									
Chronic arthritis	16	Shands	25	1930				Negative									

ARTHRITIS OF DYSENTERY

Physical and Chemical Properties.—There are no data on this subject.

Biologic Properties (Table III).—It has been pointed out that in the joints during the acute stage of this disease the total white cell count varies from 2,000 to 5,000 cells per cubic millimeter and that the granulocytes are more numerous than lymphocytes in the synovial fluid. In the convalescent stage the total white cell count is between 750 and 1,500 cells per cubic millimeter and lymphocytes may exceed granulocytes in number.

ACUTE SEPTIC ARTHRITIS

Physical and Chemical Properties (Table I).—The intraarticular pressure in cases of acute septic arthritis varied from 150 to 748 mm. of fluid. The P_H values were considerably lower in septic joint fluid, from 6.19 to 7.24. Total protein in three cases varied from 3.56 to 6.92 per cent. Sugar was definitely depressed, ranging in four cases from 19 to 43 mg. per 100 c.c. Sodium chloride varied from 556 to 577 mg. per 100 c.c. in three cases and nonprotein nitrogen from 23 to 27 mg. per 100 c.c. Icteric index in one case was 5.2.

Biologic Properties (Table V).—Chesney, Kemp and Baetjer[43] reported one case in which the total count was 1500 cells per cubic millimeter all of which were granulocytes. Culture of the synovial fluid or direct smear usually demonstrates the etiologic agent.

ACUTE GONORRHEAL ARTHRITIS

Physical and Chemical Data (Table I).—The P_H of the synovial fluid in one case was recorded as 6.97 and the icteric index in one case was 4.7.

Biologic Data.—Cultures often reveal gonococci. No further studies are recorded.

TUBERCULOUS ARTHRITIS

Physical and Chemical Data (Table II).—The sugar content in two cases was 45 and 61 mg. per 100 c.c. and the P_H in one case 7.06.

Biologic Data (Table V).—Although animal inoculation and culture in many of these cases should be positive no records were found in the literature of this procedure having been carried out. The total white cell count in seven cases varied from 2,300 to 7,300 cells per cubic millimeter. One case showed 2 per cent granulocytes, 96 per cent lymphocytes and 4 per cent monocytes. In five cases the granulocytes composed from 50 to 70 per cent of the cells and lymphocytes from 10 to 40 per cent.

SYPHILITIC ARTHRITIS

There is no data recorded concerning a chemical or physical analysis of synovial fluid in syphilitic arthritis.

Biologic Properties (Table VI).—There has been some difference of opinion concerning the possibilities of obtaining a positive Wassermann reaction in synovial fluid with a negative reaction on the blood. Four such cases are recorded by Reschke[52] and one by Chesney, Kemp and Baetjer.[43] Todd[54]

TABLE V

BIOLOGIC PROPERTIES OF HUMAN SYNOVIAL FLUID. C. SEPTIC ARTHRITIS, GONORRHEAL ARTHRITIS, TUBERCULOUS ARTHRITIS, AND ACUTE RHEUMATIC FEVER

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	WASSERMANN		ANIMAL INOCULATION	CULTURE	CYTOLOGY							GENERAL STATEMENTS
									TOTAL COUNT		PERCENTAGE					
					BLOOD	FLUID			R.B.C.	W.C.	GRANULOCYTES	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MESOTHELIAL CELLS	
Septic arthritis	1	Chesney, Kemp, and Baetjer	43	1926	Pos.	Pos.	Neg.	Negative		1,500	100					Gram positive cocci in smear
Septic arthritis	4	Habler	15	1928				Staphylococcus and streptococcus								
Gonorrheal arthritis	?	Widal and Ravault	37	1900						+	Predominate					
Gonorrheal arthritis (with fever)	1	Dopter and Tanton	23	1901						+	Predominate					
Gonorrheal arthritis (without fever)	1	Dopter and Tanton	23	1901						+		100				
Gonorrheal arthritis (acute)	1	Juillard	26	1902						+			Rare		+	
Gonorrheal arthritis (subacute)	1	Juillard	26	1902					+	+	92	6			2	R.B.C. 60 per cent W.C. 40 per cent
Gonorrheal arthritis	?	Labor and von Balogh	21	1919						± 16,000					0	
Gonorrheal arthritis	1	Habler	15	1928				Negative								

TABLE V—CONT'D

Gonorrheal arthritis (chronic infectious)	1	Forkner	45	1928				Gonococcus		3,240	87	5	8			Also found gonococci in axillary lymph nodes
Tuberculous arthritis	1	Achard and Loeper	46	1900						+	2	96	4			
Tuberculous arthritis (early)	?	Widal and Ravault	37	1900						+		+				Marked lymphocytosis
Tuberculous arthritis (late)	?	Widal and Ravault	37	1900						+	Predominate					
Tuberculous arthritis	1	Dopter and Tanton	23	1901						+		Predominate				
Tuberculous arthritis	1	Dopter and Tanton	23	1901						+	+	+			Few	Lymphocytes and polynuclears equal in number
Tuberculous arthritis	1	Julliard	26	1902						Few	36	56	8			
Tuberculous arthritis	5	Pewny	47	1921					Few	2,300 6,000	50 70	10 40				
Tuberculous arthritis	2	Pewny	47	1921						5,500 7,300	+	Predominate				
Acute rheumatic fever	1	Widal	48	1900							+					Polynuclears predominate
Acute rheumatic fever	?	Labor and von Balogh	21	1919						7,000 ±	+	+			3 ±	Polynuclears predominate
Acute rheumatic fever	8	Boots and Cullen	11	1922				Negative								
Acute rheumatic fever	?	Swift	49	1926							+					High percentage of polynuclears

TABLE VI

BIOLOGIC PROPERTIES OF HUMAN SYNOVIAL FLUID. D. SYPHILITIC ARTHRITIS, SYPHILIS WITHOUT ARTHRITIS AND CHARCOT JOINTS

DIAGNOSIS	NO. OF CASES	OBSERVER AND BIBLIOGRAPHIC NUMBER		DATE OF OBSERVATION	WASSERMANN		ANIMAL INOCULATION	CULTURE	CYTOLOGY								GENERAL STATEMENTS
									TOTAL COUNT		PERCENTAGE						
					BLOOD	FLUID			R.B.C.	W.C.	GRANULOCYTES	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MESOTHELIAL CELLS		
Syphilitic arthritis	1	Dufour	50	1901													Bloody fluid
Syphilitic arthritis (tabetic)	3	Abadie	38	1902							6	87	+		+		R.B.C. 60-80 per cent W.C. 20-40 per cent 7 per cent of monocytes, mesothelial cells and atypical cells
Syphilitic arthritis	1	Griffon and Abrami	51	1907							+	+					With treatment got change from polynuclear to lymphocyte preponderance
Syphilitic arthritis	4	Reschke	52	1918	+	+											
Syphilitic arthritis	4	Reschke	52	1918	Neg.	+											
Early secondary syphilis (no arthritis)	3	Poehlmann	53	1923	+	Neg.											
Secondary syphilis (no arthritis)	28	Poehlmann	53	1923	+	+											
Secondary syphilis	1	Poehlmann	53	1923	Neg.	Neg.											
Secondary syphilis	29	Poehlmann	53	1923	+	Neg.											

TABLE VI—CONT'D

Congenital syphilis (no arthritis)	1	Poehlmann	53	1923	+	+										
Congenital syphilis	1	Poehlmann	53	1923	+	Neg.										
Latent syphilis (no arthritis)	2	Poehlmann	53	1923	+	+										
Latent syphilis	10	Poehlmann	53	1923	+	Neg.										
Latent syphilis	7	Poehlmann	53	1923	Neg.	Neg.										
Syphilitic arthritis	4	Poehlmann	53	1923	+	+										
Syphilitic arthritis	?	Todd	54	1926	Neg.	+										
Syphilitic arthritis (early syphilis)	3	Chesney et al.	43	1926	+	+	+	Negative		17,600 24,000	50 88	12 49				Dark field examination negative
Syphilitic arthritis (late syphilis)	2	Chesney et al.	43	1926	+	+	Neg.	Negative			24 46	62 54				Dark field examination negative
Charcot joint (tabes)	1	Chesney et al.	43	1926	+	+	Neg.	Negative								Dark field examination negative
Charcot joint (tabes)	1	Chesney et al.	43	1926	Neg.	+	Neg.	Negative			56	44				Dark field examination negative
Charcot joint	7	Shands	25	1930	Neg.	Neg.		Negative		3,000 3,500	+	Predominate				
Charcot joint	2	Shands	25	1930	Neg.	Neg.		Staphylococcus viridans		3,500	+	Predominate				No association with chronic infectious arthritis
Charcot joint	1	Shands	25	1930	Neg.	Neg.		Staphylococcus aureus		3,000	+	Predominate				No association with chronic infectious arthritis

has likewise observed this phenomenon. On the other hand it is generally agreed that a joint fluid yielding a negative Wassermann reaction is frequently found in association with a positive reaction on the blood. Also it is apparent that in the presence of a positive reaction on the blood, a positive reaction on the synovial fluid is of no diagnostic significance because frequently in such patients there is no pathologic condition in the joints. Whether or not a positive reaction in an apparently healthy joint fluid of a syphilitic means that sooner or later such a case if allowed to go untreated will develop syphilitic joint disease has apparently not been determined. If one is allowed to draw an analogy here with what is known about spinal fluid under analogous circumstances it may be possible that a positive Wassermann reaction on fluid from a clinically sound joint of a syphilitic individual is of bad prognostic significance so far as the ultimate involvement of the joint in the disease process is concerned.

Chesney, Kemp and Baetjer[43] were successful in the transmission of syphilis to rabbits by intratesticular injection of synovial fluid from three cases of syphilitic arthritis occurring during early syphilis. They were unsuccessful in transmission of the disease from three other patients, two of whom had syphilitic arthritis occurring late in the disease and the third suffered from tabes dorsalis and Charcot joints. Cultures from the joint fluids of all of the above patients were negative as were also dark-field examinations of the synovial fluid.

Total white cell counts in three cases of syphilitic arthritis in early syphilis varied from 17,600 to 24,000 cells per cubic millimeter. From 50 to 88 per cent of the cells were granulocytes and from 12 to 49 per cent were mononuclear cells. In two cases of syphilitic arthritis developing late in the disease, the synovial fluid contained 27 and 46 per cent of granulocytes respectively whereas mononuclear cells were 62 and 54 per cent. One case with a Charcot joint recorded by Chesney, Kemp and Baetjer[43] showed a slight preponderance of polynuclear elements over the mononuclear cells. Ten patients with Charcot joints reported by Shands[25] contained from 3000 to 3500 white cells per cubic millimeter in the fluid and showed a mononuclear preponderance.

CLINICAL VALUE OF STUDIES ON SYNOVIAL FLUID

The question now arises as to the clinical value of studies on the synovial fluid. Table VII summarizes some of the more important points on this subject. It is apparent from what has already been said that our information for the most part is very meager and largely unconfirmed. Even with these reservations certain important scientific and clinical facts are evident. The following significant points may be deduced from the tables.

1. A sugar content under 60 mg. per 100 c.c. is almost always associated with infection in the joint.

2. A sugar content under 45 mg. per 100 c.c. is strong evidence in favor of the presence of pyogenic organisms.

3. A P_H value in the neighborhood of 7.0 is strong evidence in favor of the presence of bacteria.

4. A P_H value under 7.0 is almost certain to be associated with the presence of pyogenic organisms.

5. An icteric index of over 5.5 is practically invariably a sign that trauma is playing or has played a significant rôle in the etiology.

6. A positive Wassermann reaction in the joint fluid associated with a negative reaction in the blood is strong evidence in favor of syphilitic arthritis.

7. A positive Wassermann in joint fluid with a positive in the blood may or may not be associated with syphilitic arthritis.

8. A positive Wassermann reaction in the blood associated with a negative reaction in the synovial fluid probably represents good protection against the ultimate development of syphilitic joint disease.

9. A high leucocyte count of 11,000 or more cells per cubic millimeter associated with 60 per cent or more of granulocytes in the synovial fluid of a patient with chronic nonspecific arthritis is likely to be associated with the presence of a positive culture of attenuated organisms.

10. A leucocyte count in the joint fluid of 5,000 or fewer cells per cubic millimeter together with less than 50 per cent of granulocytes in a patient with chronic nonspecific arthritis is likely to be associated with a negative culture of the fluid.

11. The presence of large numbers of red blood corpuscles in the synovial fluid of a patient with arthritis is evidence against chronic nonspecific, tuberculous, syphilitic or acute septic arthritis and is in favor of trauma as the etiologic agent.

12. Animal inoculation is of value in the diagnosis of syphilitic arthritis occurring early in the disease.

THE NEED FOR INVESTIGATION ON SYNOVIAL FLUID

Most of the information contained in the tables is purely provisional and subject to confirmation or change. Also one is forced to admit that very little is known about either the chemical composition or cellular content of normal synovial fluid. There is much need for the application of the methods of microchemical analysis to this problem and for the further study of the physiology and cytology of normal fluid under conditions of rest and after activity of the joints and in individuals of different ages.

Almost nothing is known of the chemistry and very little of the cytology of synovial fluid in the interesting and obscure condition of intermittent hydrarthrosis. The same may be said with perhaps even more emphasis concerning the synovial fluid in acute rheumatic fever, arthritis of dysentery, acute gonorrheal arthritis, and tuberculous arthritis. In view of what is known concerning the cytology of the lesions of tuberculosis it may be predicted that the cytology of the fluid in tuberculous joints, when studied with the supravital technic may be diagnostic. One would expect to find large numbers of monocytes, typical epithelioid cells and perhaps epithelioid giant

TABLE

A PROVISIONAL GUIDE FOR THE

DIAGNOSIS	APPEARANCE	AMOUNT	SPECIFIC GRAVITY 20° C.	PRESSURE IN MILLIMETERS OF FLUID	MILLIGRAMS PER 100 C.C.			PER CENT			
					SUGAR	SODIUM CHLORIDE	NONPROTEIN NITROGEN	TOTAL PROTEIN	ALBUMIN	GLOBULIN	MUCIN
Normal	Transparent Highly viscous	From a few drops to a few c.c. Greater in resting joint	± 1.040					1.6			1.95
General edema (without arthritis)	Transparent Decreased viscosity	From few to many c.c.	1.008 1.018					± 1.39	0.45 3.90	± .025	± 0.42
Nonspecific joint effusions	Transparent, bloody, or cloudy Decreased viscosity	From few to many c.c.		68 2720.	72 119	573 623	19 33	3.54 6.33	2.26 3.72	0.31 2.45	0.41 0.65
Intermittent hydrarthrosis	Colorless or cloudy	From few to many c.c.									
Traumatic effusion and traumatic arthritis	Often bloody, yellow, or cloudy	Variable		0 700	58 103	584 674	21 34	3.64 6.33			
Chronic nonspecific arthritis (chronic infectious, atrophic, hypertrophic, rheumatoid, deformans, etc.)	Transparent, cloudy, or yellow. Usually decreased viscosity	Variable	± 1.017	68 395	73 132	409 633	22 43	3.92 7.25			0.27 0.38
Acute rheumatic fever	Colorless, cloudy, or slightly yellow	Variable									
Arthritis of dysentery		Variable									
Acute septic arthritis	Cloudy, often yellow. Decreased viscosity	Large or small		150 748	19 43	556 577	23 27	3.56 6.92			
Acute gonorrheal arthritis	Cloudy, often yellow. Decreased viscosity	Large or small									
Tuberculous arthritis	Cloudy, often milky yellow	Moderate			45 61						
Syphilitic arthritis (early syphilis)	Yellow, often cloudy	Usually large									
Syphilitic arthritis (late syphilis)	Yellow, often cloudy	Variable									
Tabes (Charcot joint)	From straw to deep red color	Often large									

VII

STUDY OF SYNOVIAL FLUID

P_H	WASSERMANN: BLOOD	WASSERMANN: FLUID	TOTAL WHITE CELL COUNT	RED BLOOD CORPUSCLES	DIFFERENTIAL COUNT: GRANULOCYTES	DIFFERENTIAL COUNT: LYMPHOCYTES	DIFFERENTIAL COUNT: MONOCYTES	DIFFERENTIAL COUNT: MACROPHAGES	DIFFERENTIAL COUNT: MESOTHELIAL CELLS	CULTURE	ANIMAL INOCULATION
7.4	Neg.	Neg.	± 50	Probably absent or rare	± 5	?	± 58	± 30	± 3	Negative	Neg.
± 7.34	Neg.	Neg.	0 50	None				+	+	Negative	
7.21 7.58	Neg.	Neg.	Variable							Negative	
7.37 7.47	Neg.	Neg.			±	+				Neg. or positive Strep. viridans Staph. albus Staph. aureus	
7.13 7.68	Neg.	Neg.		Many	1 100	2 33	± 5		0 98	Neg. or positive Strep. viridans Staph. aureus	
7.0 7.9	Neg.	Neg.	*Bacteriologically Positive Fluids*							Neg. or positive Strep. viridans Strep. hemolyticus Strep. nonhemolyticus Staph. aureus Staph. albus Gonococcus Diphtheroid	
			± 11,000	Rare	± 61	± 19	± 15	± 3			
			Bacteriologically Negative Fluids								
			± 4,800	Rare	± 48	± 27	± 21	± 3	± 1		
7.27 7.42	Neg.	Neg.	± 7,000		Predominate	+			± 3	Negative	
	Neg.	Neg.	750 5,000		Predominate in acute stage	Predominate in convalescent stage					
6.19 7.24	Neg.	Neg.	Often very high		± 99					Usually positive for infecting organism	
± 6.97	Neg.	Neg.	Often very high		Predominate					Gonococci may often be cultured	
± 7.06	Neg.	Neg.	2,300 7,300		+	+	?				Often positive
	Pos. or Neg.	Pos.	17,000 24,000		50 88	12 49				Negative Dark-field examination also negative	Positive
	Pos. or Neg.	Pos.			24 46	54 62				Negative Dark-field examination also negative	Neg.
	Pos. or Neg.	Pos. or Neg.			± 56	± 44				Negative Dark-field examination also negative	Neg.

cells, the so-called Langhan's giant cells. Syphilis of the joint may also show such changes, but can easily be differentiated by the history, Wassermann reaction, and by animal inoculation.

It is very significant as regards the bacteriology of joint exudates that attenuated organisms can, by persistent, careful, patient investigation, be cultured from a high percentage of cases with chronic, nonspecific arthritis. The recent contribution of Shands[25] in which the same types of organisms have been grown from Charcot joints, from cases of traumatic arthritis and from cases of intermittent hydrarthrosis would tend to support a theory that in the etiology of arthritis there are several factors involved. One factor is undoubtedly injury to the joint structures whether that be by direct trauma, by trophic, metabolic of deficiency disturbances, or as the result of congenital defects. Another important factor, at least in a fair proportion of cases, is an actual invasion by organisms of one or another type. There is an urgent demand for further work in the biologic as well as the chemical analysis of synovial fluid which may help to prevent and to treat satisfactorily the commonest sort of ailment that man is susceptible to, chronic disease of joints.

SUMMARY AND CONCLUSIONS

1. Physical, chemical and biologic data on the synovial fluid in health and disease have been reviewed in detail and tabulated for comparison.

2. A study of the synovial fluid in arthritis provides important differential diagnostic points. It yields information which approaches in importance that obtainable from the study of cerebrospinal fluid.

3. The need for further research on normal and pathologic joint fluid is stressed and the direction for such investigations is indicated.

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CHRONIC ARTHRITIS

I. A Basic Diet for Chronic Arthritis

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IMPORTANCE of the Subject.—There is perhaps no subject to which the medical profession of today is giving much attention as to arthritis. This will undoubtedly continue to be the case for years to come, for research has proved that a relatively large percentage of the population is suffering from the disease, and its cure or mitigation is therefore a matter of vital social and economic significance. This and other articles to follow containing practical considerations of the problem of chronic arthritis are based upon the assumption that arthritis is, in many cases, curable, and that under the supervision of physicians who have specialized in its study it presents the same possibilities for a favorable prognosis as are found in any other curable disease.

The Purpose of These Articles.—It is the plan in this series of articles, to present the results of many years of practical clinical endeavor in the treatment of arthritis. Many aspects of the etiology and therapeusis of the disease will be considered systematically. The rôle of diet in arthritis, the relation of the colon and colonic therapy, the importance of foci of infection, menopausal arthritis and its endocrinologic aspects, vaccine, sera and drug therapy, the employment of physiotherapy and hydrotherapy, posture, will all be considered, not as separate entities, but as correlating forces in the treatment of arthritis. No one type of therapy can be held forth as a panacea for every type of arthritis, for the reason that its etiologic roots are too deeply anchored in the warp and woof of the human mechanism. The successful treatment of arthritis demands that this be kept in mind. A broader understanding of the physiology, biochemistry, and bacteriology of the human mechanism is essential to the physician who is dealing with the problem of arthritis. Single-minded faddists have no proper place in the modern attack on this disease.

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History of the Disease.—Chronic arthritis is not a new disease. Its historical frontiers date back to the Mesozoic Age, centuries prior to the earliest recovered human fossils. Because it etches its ineradicable imprint on bone, a tissue easily fossilized and which defies the ravages of time, arthritis has been traced to the early Age of Reptiles, 15,000,000 years ago. Since that time the paleontologic evidence of the disease has become increasingly abundant. It is not possible in an article of this kind to present a complete history of the disease, but to portray arthritis adequately as it exists today it is important to consider briefly the high lights of its history in order to realize how deep-rooted it is in the biologic history of man.

Arthritis was a well-known and even common ailment in ancient Egypt. Flinders Petrie found undisputed evidences of the disease in the skeletons unearthed in the tombs of Gurob, which date back to 1300 B.C. While Hippocrates was elucidating his Aphorisms on gout 300 years before the Christian era, Erasistratus was employing modern hydrologic methods of treatment for arthritis. Two centuries later Pliny and Seneca were calling the ancient Romans to account for their riotous living and attributed the prevalence of arthritis to excesses of diet. Aix Les Bains was almost as popular a cure for arthritis at the dawn of the first century A.D. as it is today. Celsus and Galen advocated bleeding, purgations, and local applications to the joints of their second century patients.

Classifications.—No other disease group has had as many attempts at classification as has arthritis. No attempt will be made here to give in detail the classifications of Charcot, Virchon, Sauvage, Cullen, Landre-Beauvais, and a host of others. In 1827 Scudamore first recognized the importance of the inflammatory changes in the fibrous tissue in articular and periarticular structures, and two years later Cruveilhier for the first time clearly differentiated ostearthritis as a distinct disease entity. Garrod in 1833 was the first to demonstrate an excess of uric acid in the blood of gouty subjects and in 1890 recognized two distinct types of arthritis. This classification still has considerable vogue. The ensuing years saw many futile attempts to bring order out of chaotic classifications and even today there is much confusion in nomenclature. This fact, added to the still obscure etiology of the disease, makes the subject an exceedingly difficult one to investigate and treat.

Goldthwait classified chronic arthritis into (1) infectious, (2) atrophic, and (3) hypertrophic.

In 1909 Nichols and Richardson, in a masterly monograph based on a series of 65 cases of chronic nontuberculous, deforming arthritis, most of which was accompanied by pathologic examination of postoperative or autopsy specimens, simplified the classification of arthritis, on the basis of morphologic changes, into two main types (1) proliferative or atrophic or ankylosing and (2) degenerative or hypertrophic or nonankylosing, corresponding respectively to the atrophic and hypertrophic classification of Goldthwait.

In 1922, the British Ministry of Health adopted a classification which in essence agrees with that of Nichols and Richardson, using, however, the term rheumatoid arthritis for the atrophic type, and ostearthritis for the hypertrophic type.

There are at present at least seven different types of classification sponsored by recognized authorities. This flat difference of opinion bears eloquent witness to the obscurity which still seems to surround our knowledge of the etiology, pathogenesis and treatment of this disease.

Statistics.—A study of the following data cannot fail to impress one with the tremendous urgency of the problem of arthritis:

Sweden. 9.1 per cent of all cases causing "permanent pensionable invalidity" are due to articular rheumatism.

England. Under an all-embracing classification of rheumatic disease, rheumatism is responsible for one-sixth of the entire industrial invalidity, necessitating an expenditure of approximately $10,000,000 a year for payments of sick benefit and a loss of working time amounting to 3,000,000 weeks a year. In 1922 about 90,000 patients applied for medical advice for chronic arthritis. Of these about 40,000 were severe cases and 25,000 of moderate severity and 25,000 were early cases.

Denmark. In 1923, 14 per cent of 7,297 persons receiving total invalidity pensions suffered from some form of chronic arthritis.

Germany. Here Arnold Zimmer has demonstrated, from statistics of the State Insurance Institutions, an enormous invalidity attributable to chronic rheumatic disease. A Research Institute in Rheumatism, to work with the University of Dusseldorf, has been established.

This widespread prevalence of arthritis is just as evident in other European countries as in those quoted.

There are no complete accurate statistics available for the United States, but there is no doubt in the minds of many physicians who have hospital and clinic facilities that a great percentage of patients applying for treatment are sufferers from some form of arthritis. The consensus of opinion in the larger clinics in New York City is that about 20 per cent of patients applying for treatment are patients who have arthritis.

An Organized Crusade.—In Europe, national and international organizations are actively engaged in the study of arthritis. The International Committee on Rheumatism, with headquarters in Amsterdam, is directing the problems of the study, treatment, and prevention of arthritis. In this country, in 1925 the Hospital for Ruptured and Crippled of New York City organized an Arthritis Clinic, the first to be devoted solely to the study and treatment of arthritis. A group of specialists in the various branches of medicine and surgery were assembled in a single unit, aided by the laboratory and technical staff of the hospital, to determine the relationship of their specialties to the problem of arthritis. In 1926 an American Committee under the chairmanship of Dr. Ralph Pemberton was formed to cooperate with the European groups in the crusade against arthritis.

The result of this awakened interest has manifested itself in the altering of the prognostic viewpoint. For many years this disease was regarded as hopelessly chronic, both by the profession and the laity, and this pessimistic attitude led to an apathetic indifference on the part of the profession to the consideration of the etiology of the disease and its many legitimate methods of therapy. For years patients were thus driven to cultists and faddists who

have profited by the lack of interest on the part of the medical profession with respect to arthritis. The disease is admittedly a difficult one with which to deal. Its classification is still under consideration, its etiology obscure, its stubbornness in yielding to treatment notorious. These factors have long constituted an efficient barrier to the interest of the practitioner, who often chooses to devote his time and energy to the more spectacular and perhaps better understood fields of his art in which results are more easily achieved.

This unfortunate situation is, however, rapidly being corrected. Through the influence of the organized groups both here and abroad, clinics for the exhaustive study and treatment of arthritis have been established in nearly all the large cities of this country. These clinics, arthritis units, combine the skill of the physician, general surgeon, orthopedic surgeon, roentgenologist, otolaryngologist, gynecologist, urologist, dentist, physiotherapist, together with trained laboratory technicians and nurses, to provide for the patient a formidable armentarium in the battle against arthritis. Able research workers are giving to the profession the results of their intensive efforts in monographs and in more pretentious volumes.

Thus, the entire attitude of the profession and the laity is undergoing a change from that of regarding arthritis as involving a hopeless, painful invalidism, to a more optimistic view. Perhaps there is no one element more essential than this change of attitude for successful treatment of this dreadful malady.

Causes of Arthritis.—It is generally admitted that arthritis may find its cause in dental or tonsillar sepsis or in infections of the paranasal sinuses, gall bladder, appendix, prostate, cervix, or adnexa. These foci may, per se, be the causative agent, or, as considered by many eminent students of the disease, merely constitute the spark which sets the fire raging. Heredity, disorders of metabolism, pregnancy, the menopause and intestinal disorders, vitamin or glandular deficiency are all etiologically important. The American Committee for the control of rheumatism, as quoted by Pemberton, its Chairman, has placed itself on record as "believing that the underlying causes of arthritis are often further to seek, and are to be found, in part at least, in that background determined by heredity, constitutional make-up, the equilibrium of the nervous system, chemical, and other toxins of imponderable nature, and finally the conditions of the environment." Any of these causes may exist singly or in combination and their presence must be established unequivocally and treated on their own merits. This demands a thorough and careful work-up of each case, often necessitating the consultation of specialists to establish the presence or absence of many of the contributing factors in the disease.

Classificction Used in These Papers.—While the classification of arthritis, on a morphologic basis as delineated by Nichols and Richardson, has accomplished much to clarify the issue, yet for practical clinical consideration it was found wanting. From the standpoint of etiology and as a guide to the treatment, it was decided by the authors to adopt the following classification: (1) infectious, (2) metabolic, and (3) mixed.

Under the first group were placed all cases in which demonstrable foci of infection were the undoubted etiologic factors. The second, or metabolic group,

comprises cases in which heredity, disorders of metabolism, intestinal disorders, vitamin or endocrine deficiency, pregnancy or the menapause seem to be the dominating etiologic factor and in which no foci could be demonstrated. In this group gout is considered as a form of metabolic arthritis. In the third group, in which the majority of cases fall, are placed cases which show characteristics of both the foregoing classes. Quoting Glover in his *Report on Chronic Arthritis* for the British Ministry of Health: "For example, suppose the diagnosis of gout, the most undoubtedly metabolic disease of this group, the second duty, the search for the infecting focus, is a claimant, as ever, for in a large proportion of cases of gout an infective focus plays an important rôle in activating the metabolic process and in precipitating attacks." Of course, these groups are further classified as to whether they are acute or chronic. This purely clinical classification will be retained throughout this series of articles.

SOME PRACTICAL CONSIDERATIONS IN THE FORMATION OF A BASIC DIETARY FOR ARTHRITIC PATIENTS

Glover, in a *Report on Chronic Arthritis* for the British Ministry of Health in 1928, makes the following statement: "Diet is a most important part in the treatment of chronic arthritis. The indications are more various than in almost any other form of treatment."

No absolute rule can be laid down regarding the diet. The special features of each case should receive careful study. Simplicity and moderation are of the utmost importance.

After an exhaustive and careful perusal of the literature on the regulation of diet in arthritis and after many years of dietary regulation of hundreds of clinic and office patients, it was found that the ideal basic diet for arthritic patients should have the following characteristics:

1. Low caloric value
2. Low carbohydrate value
3. Low protein value
4. Low purin value
5. Adequate vitamin content
6. Elasticity
7. Availability

1. *Low Caloric Value.*—In the Third Century A.D. Caeleus Aurelianus, who affirmed that arthritis was caused by heredity, indigestion, over-drinking, debauchery, and exposure, advocated an abstemious dietary for arthritis. Since then there has been a consistent agreement of authorities that a low caloric intake is advisable, even necessary, to the successful treatment of arthritis.

It has been abundantly proved by experience that in most patients with arthritis a sharply reduced diet, almost a starvation diet, is beneficial in bringing about greater freedom of movement, comfort of the patient, and actual reduction of either high uric acid or sugar or both in the blood. Dr. Ralph Pemberton undoubtedly deserves the major portion of credit for drawing the attention of the medical profession to this fact.

Clinical experience of the authors agrees with that of many eminent students of arthritis that in the vast majority of cases there is an optimal level of caloric intake, definite for each individual, below which the symptoms of the disease tend to decrease and above which they are aggravated and become persistent. By careful observation this level of caloric intake must be adjusted for each individual. The medical profession is apt to forget that no two individuals of the human race are any more alike in other respects than they are in their finger-prints.

Kraus, Bruysch and Mueller observed a general and considerable improvement in the cases of chronic arthritis in Germany during the war, when the food shortage was acute.

Again, it has often been shown that patients with chronic arthritis, who come to operation for some intercurrent pathology, are definitely relieved of their arthritic symptoms during their postoperative convalescence, with its concomitant restriction in food intake. This improvement is often mistakenly credited to the operation rather than to enforced starvation.

Drastic reduction in caloric intake in average uncomplicated cases of arthritis is perfectly safe provided and only provided the course of the patient's progress and weight is carefully supervised. Additions to the dietary can and should be made as rapidly as the condition of the individual patient warrants. In this manner it is possible to bring the diet up to the optimum level at which the patient's metabolism operates, and at which he is best able to carry on with a minimum of discomfort on the one hand and the maximum permissible energy on the other. In asthenic individuals, or in patients whose arthritis is complicated by nephritis, hypertension, diabetes, etc., the dietary must be controlled with these concomittant factors in mind.

Regardless of the etiologic factors operating in any individual case, it is certain that the metabolism of the sufferer from arthritis has been either overloaded or impaired. This is obvious by the very nature and symptoms of the malady. This metabolic deficiency may be due to a disturbance or interference in the capillary circulation, as recently pointed out by Pemberton and his coworkers, or it may take on a much larger physiologic and biochemical aspect, with probable involvement of the sympathetic nervous system. In any event, by lowering the caloric intake and thereby relieving the metabolic burden, the tissues of the body are given an opportunity to relieve themselves of this overload and to operate on a more nearly normal metabolic level. It seems logical to infer that when the organism is laboring under an increased metabolic burden, it is rational therapy to lighten that load.

Fats are not inimical to the arthritic patient, but since even small amounts will raise the total caloric value, their careful restriction within the caloric limits of the diet is desirable.

The Colon.—The importance of the rôle of the colon in arthritis will be dealt with in greater detail in a succeeding article, but it is necessary to call attention here to some outstanding facts. It is generally conceded that arthritis may often be caused by bacterial proliferation in the body, particularly in the colon. A reduction of caloric intake must of necessity tend to reduce the volume of the colonic content which acts as a most excellent culture medium for

bacterial growth. Thereby is reduced not only the number of bacteria in the colon but also those products of putrefaction generated by the action of bacteria on the feces, which may cause added mischief to an organism already physiologically below par. This is especially true where the reduction of caloric intake is considerable.

In the last decade a great deal of attention has been centered upon the intestinal tract, especially the colon and its relation to arthritis. Colonic therapy is becoming an increasingly employed method in the management of arthritis, and rightly so, for there is no doubt that, in a great number of cases, this mode of treatment is highly successful. It is therefore evident that it would be irrational to concentrate on the removal of undesirable and noxious intestinal contents without first regulating the intestinal intake in the matter of food. The character and amount of colonic content is determined primarily by the nature of the food ingested. Fletcher and Graham have recently demonstrated concomitant colonic abnormalities in patients with arthritis who were markedly improved by dietetic treatment with coincident improvement in the arthritis.

It is appropriate at this point, before beginning an analysis of blood chemistries of patients with chronic arthritis, to emphasize the fact that by far the greater majority of patients encountered in clinic and private practice have been under some form of medical, lay or self-imposed régime, for some length of time prior to admission. This has included such forms of therapy as baking and massage, Hot Spring cures, dietary regulation (especially meat restriction), and the taking of drugs of the cinchophen or salicylate groups which, as is well known, stimulate the kidneys to eliminate uric acid. It would, therefore, be difficult to estimate the blood chemistry values of these patients prior to such therapy at the onset of symptoms.

2. *Low Carbohydrate Value.*—In a careful survey of about 1200 case histories and charts of patients with arthritis, both in clinics and office practice covering about five years, it was found that a great number of these patients had high blood sugar on admission. In the past five years of 425 consecutive patients suffering from arthritis seen in office practice who had blood chemistries done, 136 or more than 32 per cent had blood sugar values of 120 mg. or more. Of 732 clinic patients with arthritis, 278 or 32 per cent plus, had blood sugar values ranging above 120 mg., which was considered the upper limit of normal.

BLOOD SUGAR

OFFICE CASES Below 110 mg.	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-189	190-199	200 and up	Total cases
152	133	80	27	9	12	4		3		1	421

HOSPITAL CASES*

Below 110 mg.	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-189	190-199	200 and up	Total cases
285	169	165	63	19	10	7	1	4	2	7	732

*These cases were seen in the Clinic for Arthritis, Hospital for Ruptured and Crippled, New York.

None of the patients proved to be diabetic. It was further noted that as treatment progressed and the symptoms cleared up, the blood sugar values

tended to approach normal. This was true only when patients were rigorous in the observance of their diet. Deviation from dietary regulation was attended with a recurrence of symptoms and a return of the blood sugar values to their former high levels. Blood samples were all taken in the morning and determinations were made immediately after the blood was obtained.

In Pemberton's article on Arthritis in *Nelson's Encyclopedia,* the following appears: "It appears at present useful, in undertaking treatment on the basis of reduced caloric intake, to reduce the carbohydrates most, the proteins somewhat less, and the fats least of all, although it is also essential that the total caloric intake be reduced to a certain definite level. Carbohydrates constitute the chief caloric yielding substances of our diet under average conditions of life. Any attempt to reduce the total calories must therefore be with carbohydrates."

There is a general agreement among students of arthritis, that with many patients suffering from this disease, there is a delay in the removal of the sugar ingested from the circulating blood. This lowered sugar tolerance is more or less variable with the degree of activity of the arthritic process. That it is not due to pancreatic deficiency was demonstrated by Cecil, Barr and Du Bois, who showed by calorimetric studies that the carbohydrate metabolism of patients with arthritis proceeds normally. Arthritis is not a part of the diabetic syndrome even though infections frequently occur in it. Race demonstrated that the sugar tolerance curves of chronic arthritis and mild diabetes were similar and that the presence of some common factor was thereby suggested, but that they are distinct entities is shown by the fact that in arthritis there is no tendency to the formation of acetone or diacetic acid in the urine. The exact nature of the physiologic dysfunction responsible for this delayed sugar removal is not well understood. Pemberton believes that this delay is "brought about by some influence which causes vasoconstriction or some comparable state of the finer blood vessels in some of those tissues whose function it is to remove glucose, oxygen and presumably other substances from the circulatory blood."

Arthritis is not the only nondiabetic disease in which a delayed sugar removal is encountered. It is also found in certain (1) thyroid dysfunctions, (2) furunculosis and eczema, (3) neuroses, and (4) unrecognized inflammatory processes or focal infections; but this phenomenon is more frequently coincidental with arthritis than with any other disease. This is especially true in cases in which demonstrable foci of infection occur, and furthermore it was shown by Pemberton that the rate of sugar removal showed an abrupt change toward the normal level after removal of the apparently causative foci of infection. There are, however, a certain number of patients with arthritis who show a lowered sugar tolerance in whom, even after the most painstaking investigation no foci can be demonstrated. It is also true that this lowered sugar tolerance is susceptible to rigid dietary regulation even in the presence of a surgical focus.

Symptomatic improvement of patients with arthritis who have demonstrated delayed glucose removal is accompanied by a return to approximately normal tolerance levels. It would seem probable, in view of the foregoing observations, that a restriction of carbohydrate intake might tend to lift the burden

from the system which had demonstrated a physiologic dysfunction in the nature of disturbed rate of carbohydrate removal.

It is common knowledge that patients with gout are frequently subject to an amylaceous dyspepsia. This type of carbohydrate indigestion has often been encountered by us in treating patients with metabolic arthritis, and it has been our experience as well as the common experience of other workers that this type of case is most frequently aided by a restriction of carbohydrate intake.

3. *Low Protein Value.*—After carbohydrate reduction, the next important foodstuff to be considered is protein. Experience with dietary regulation of arthritis proves that a low protein intake is desirable. The reduction of protein should be accomplished by curtailing those foods which are subject to putrefactive decomposition in the colon. The chief offenders in this group are meats and fish. However, it is essential to preserve for the patient the minimum protein allowance of from 0.7 to 1.0 gram per kilo of body weight. This protein should be chiefly in the form of milk, eggs, cheese. Meats or fish may be included in the diet once a day or preferably once every other day, only to make the diet more acceptable to the patient and to secure his cooperation. In the zeal to eliminate the disease the individual is often forgotten. Ruthless dietary restriction will more often than not be provocative of antagonism on the part of the patient, who very often, especially in the metabolic cases, has developed a life-long habit of indulgence. If, by the inclusion in the dietary of carefully selected and restricted meats and fish, the monotony can be relieved, the hearty cooperation of the patient secured, more progress will be achieved than by causing resentment by strict unrelenting dietary control. The success of dietary regulation depends a great deal on persistence. Often, after months of treatment with drugs, irrigations, bakings, massage, vaccines, focus eliminations, etc., when apparently nothing has been accomplished in the way of clinical improvement, patience and perseverance in the dietary will bring definite amelioration. In order to be assured of the patient's cooperation in this long extended period of dietary control the diet must be, within limits, acceptable to the patient and practical in its home preparation or other availability.

4. *Low Purin Value.*—Another important aspect of the protein regulation in the treatment of arthritis is its relation to the problem of uric acid and purin metabolism. In Glover's report on arthritis to the British Health Ministry the following statement is found: "It appears well established that the uric acid in the blood is increased in practically every case of gout and in many cases of ostearthritis." J. Race has recently published the results of the examination of the blood in 662 patients in the Devonshire Hospital, Buxton, showing that there was marked increase in 100 per cent of cases of gout in 79 per cent of male patients with ostearthritis and 58 per cent of female patients. Maizels and Payne found "the blood uric acid abnormally high in 8 out of 15 cases of rheumatoid arthritis investigated at Guy's Hospital in 1927." Folin and Davis in 1915 reported high uric acid findings in arthritis. Pratt in 1918 and Horowitz in 1926 found high blood uric acid values in nongouty arthritis. These results have been more than adequately substantiated in the experience of the authors, especially in cases falling in the metabolic or mixed groups. In a

series of 731 consecutive cases of arthritis seen in clinic practice at the Hospital for Ruptured and Crippled, 381 or more than 50 per cent showed a decided increase in blood uric acid levels, in spite of the fact that more than 90 per cent of these patients had been on dietary restrictions with especial reference to meat and had been taking salicylates or some form of cinchophen both of which tend to lower blood uric acid values. The upper limit of normal for blood uric acid was set at 3.5 mg. per 100 c.c. Of these 731 patients, 149 or about 20 per cent were males, and 582 were females, or 24 per cent and 75 per cent respectively.

In a series of 425 consecutive cases of arthritis seen in office practice, 250 or more than 59 per cent of the patients showed increase in blood uric acid. Of these 425 patients, 138 or 32 per cent were male and 287 or 67 per cent were female. And what is strikingly important is that in the vast majority of clinic and office cases of arthritis, more especially in the metabolic types, it has been found that the amount of clinical improvement varies with the blood uric acid value obtained as a result of treatment. Symptomatic improvement proceeds as the blood uric acid values approach normal levels. This phenomenon has been encountered so frequently as to make it almost possible to utilize the blood uric acid values as a guide to the patient's progress. It is to be remembered that the clinic and office patients mentioned above represent consecutive cases and all types, metabolic, infectious and mixed, and were all ambulant cases. In this country, one does not encounter the high blood uric acid figures found so frequently in gout, because pure gout, as seen in England and the Continent, is comparatively rare in the United States.

URIC ACID

	BELOW 2.5 MG.	2.5-2.9	3.0-3.4	3.5-3.9	4.0-4.4	4.5-4.9	5.0-5.4	5.5 AND UP	TOTAL
Office cases	12	42	121	112	96	25	9	8	425
Hospital cases	29	86	235	172	151	48	6	4	731

In view of these facts it would be intelligent therapy to limit the intake of protein not only because by its specific dynamic action it increases the metabolic load, but, according to McLester, also because it increases the output of uric acid; and because purin bases, which are the precursors of uric acid, are derivatives of the metabolism of certain particular proteins.

It is an erroneous assumption that uric acid is a product of the metabolism of all proteins. It is only from the proteins which are rich in these compounds of nitrogen and phosphorous known as nucleins or nucleoproteins and which in their decomposition yield nucleic acid, that uric acid and purin bases are derived. Nucleins, which, as the name implies, are derived from the nuclei of disintegrated cells, come from two sources. First, from cell nuclei ingested in some kinds of food (exogenous nucleins), and secondly endogenous nucleins from the cells of the body, which are constantly undergoing destruction as the result of general tissue activity. In the normal course of events, nucleins, both endogenous and exogenous, are broken down by a series of ferments, first into intermediate "purin bodies" such as guanin, adenin, hypoxanthin and xanthin, and eventually into uric acid and urea, in which two forms they are ultimately excreted. These proteins are found in greatest abundance in animal tissues

made up largely of nuclei, i.e., liver, pancreas, thymus, kidneys. Other food stuffs which yield high uric acid values are, anchovies, sardines, herring, carp, lentils, and squab.

PURIN CONTENT OF VARIOUS FOODS

(J. Schmid and G. Bessan)

100 GRAMS	URIC ACID IN GRAMS
Beef	0.111
Veal	0.114
Mutton	0.078
Pork	0.123
Liver	0.279
Kidney	0.240
Sweetbreads	0.990
Chicken	0.087
Herring	0.207
Sardines	0.354
Anchovies	0.465
Spinach	0.072
Shell beans	0.081
Lentils	0.162
Oysters	0.087
Boiled ham	0.075
Fresh salmon	0.072
Lobster	0.066

It is this type of protein, that is responsible for high exogenous purin values, whose intake it is wise to curtail. It has been frequently demonstrated that the feeding of large amounts of nucleoproteins has been followed by an attack of gout. Dr. George Minot has reported that many of his cases of pernicious anemia treated successfully upon a large liver diet have developed hypertrophic arthritis. Quoting Llewellyn, "Even if we entirely eliminate all purin substances by restricting the diet to purin-free foodstuffs (bread, milk, cheese, eggs, and butter) purin in the form of uric acid is still excreted in the urine. To this variety the term endogenous purin is applied, for the continued excretion of purin on such a diet is explicable only on the view that they are derived from the wastes of the tissues, the daily wear and tear of the cells. In other words, it is the outcome of the katabolism of the nucleoproteins of the body tissue."

It would indeed be foolhardy to add to the food intake, purins which act only to increase the metabolic burden of an organism whose blood uric acid is in many cases abnormally high and which is already producing and excreting uric acid by the katabolism of its own tissues.

We are well aware of the fact that this study of the blood chemistry of chronic arthritis revealed no abnormally high blood sugar or blood uric values. The contention is not made that high blood uric acid or sugar cause arthritis, but they do indicate a disordered metabolism. This added to perhaps colonic stasis, or menopause, or infection or any of the aforementioned possible etiologic factors is sufficient to precipitate an attack. The contention is not made that proper diet alone will always or completely alleviate arthritic symptoms, but the successful treatment of arthritis will and must include dietary measures to restore, as far as possible, the normal metabolism as reflected in the blood sugar and blood uric acid. Failing this, all other measures directed to any other concurrent etiologic factor are liable to failure.

5. *Adequate Vitamin Content.*—In 1927 M. J. Rowlands, in a communication to the Royal Society, developed the thesis that rheumatoid arthritis is a deficiency disease due in part to an inadequate Vitamin B content. Rowlands placed his patients on a concentrated Vitamin B diet and reported considerable clinical success from the treatment. H. A. Ellis also contends that rheumatoid arthritis is a deficiency disease, but considers the deficiency as a biochemical problem concerned with the utilization of phosphoric acid and its radicals; so that a deficiency of both Vitamin B and D is associated with it. Lovell Langstroth, in a recent examination of American dietaries based on a careful study of 501 general cases with controls, makes an eloquent plea for the inclusion of "protective foods" in the dietary because of their vitamin content. In this study it was demonstrated that the average American diet was "low in vitamin and residue, high in calories, in carbohydrate and in its ratio of acid to alkaline ash forming foods and contained a large proportion of concentrated foods." In the disease groups studied were hypertension, myocardial degeneration, arteriosclerosis, arthritis, chronic gastrointestinal disease, diabetes and the occasional unexplained headache. Incidentally 75 cases of arthritis were studied, of which 65 were degenerative arthritis, 8 proliferative arthritis, and 2 infectious arthritis. Many of the 65 cases presented only early changes manifested by tenderness and aching of the joints.

The conclusions arrived at on the basis of these investigations were interesting and important. It was found that 74 per cent of patients with degenerative or proliferative arthritis, the metabolic group, were improved or completely relieved by diet containing the required protective foods. The cases of infectious arthritis were improved by elimination of the foci. The loss of weight occasioned by the dietary was considered as a possible factor in the relief afforded, especially in the lower weight-bearing extremities, but the major rôle of the quality of food was demonstrated by the general improvement evident in the functions of the alimentary and circulatory systems as well as objective changes in the superficial tissues surrounding the affected joints.

The protective foods which are so rich in vitamin content are eggs, milk, fruit, vegetables and especially lettuce. Lanstroth recommends a diet of 2,147 calories of which 70 per cent are these protective foods.

We have long been in full accord with these observations with respect to adequate vitamin content in the dietary of patients with arthritis, and in the basic diet advocated necessary provision has been made for ample representation of the protective vitamin containing foods. They have instituted a clinical study of the value of diets rich in Vitamin B, using well-known commercial preparations which are known to contain relatively large amounts of this Vitamin B. These substances are used in conjunction with the diet, and the results, so far, are gratifying—although it is too early to make any definite conclusions. Another series of clinical experiments using liver extracts is under way and will be reported on at a later date.

A great deal has been written about the rôle of vegetables in a diet for arthritis. It is axiomatic that the best diet for any disease entity is the one which causes the least indigestion. All-embracing generalities such as "eat all green vegetables," "eat all vegetables which grow above the ground," etc.,

have been recommended. Cabbage, brussels sprouts, cauliflower and broccoli are all almost purin free and meet with nearly all requirements, but their effect on the digestion and elimination of many patients is so distressing as to make their ingestion at the beginning of treatment undesirable, even noxious. Spinach, beans, peas, lentils have relatively high purin values and should be partaken of sparingly. They may be utilized later in the course of dietary control as addenda. Potatoes, turnips, carrots, rice, parsnips and beets have relatively high carbohydrate values and should not be included in a *basic* diet. They also may be added later in treatment, although parsnips and turnips might well be ignored entirely because of their notorious association with indigestion in certain cases. It is therefore advisable to select carefully the vegetables to be placed on a dietary for arthritis rather than to allow a wide choice in the kind and amount of vegetables to be used.

The inclusion of fruits, especially fresh fruits, in a dietary for patients with arthritis is essential. The popular bogy of "fruits produce acid" has long since been robbed of its terror. They form, when confined within the caloric and carbohydrate limits of the diet, a most valuable adjunct to the diet because they contain no purins, are easily digestible, make the diet more attractive and palatable, lend bulk, without too greatly increasing the caloric value, and form a valuable source of vitamins.

6. *Elasticity.*—It must be borne in mind that concomitant pathology is often found in patients with arthritis. Associated with arthritis, the disease entities often encountered are arteriosclerosis, hypertension, chronic nephritis, myocardial degeneration, cardiac valvular disease, obesity, diabetes and chronic gastrointestinal disease.

Any basic diet prepared for patients with arthritis must, of necessity, be so elastic as to be readily adaptable to any concurrent pathology which the patient may present.

7. *Availability.*—The diet must be so contrived as to be easily available in restaurants, hotels and trains and must be easily adapted to preparation in the home without upsetting the normal kitchen régime. Any deviation from these requirements will make it difficult to secure whole-hearted cooperation from the patient.

The diet herewith presented is a basic diet which meets, in so far as possible and practical, the foregoing requirements, and is one on which practically any type of individual may carry on for a short period at least. Any patient with arthritis, regardless of weight or condition, may be placed on this diet with impunity for a period of ten days. During this interval the patient is most carefully observed and the diet then altered as the progress, general condition, weight, blood chemistry, and concomitant pathology of the patient indicates.

It might be well to note here that this diet is utilized in conjunction with other indicated procedures such as colonic irrigations, vaccine therapy or physiotherapy. It was not deemed wise to curtail this diet below its present caloric levels, considering the strain placed on the patient by these other therapeutic measures.

If the diet is to be used without other concurrent more or less strenuous form of treatment, it would perhaps be wise to limit the protein intake below the level indicated in the diet.

Basic Diet

Breakfast

	PROTEIN	FAT	CARBOHYDRATES	CALORIES	URIC ACID	PROTECTIVE FOODS	NONPROTECTIVE
Choice of one of the following fruits:							
One orange, sliced or as orange juice, no sugar	6.2	2.3	87.1	96		96	
or							
Grapefruit (half), no sugar	9.7	5.6	124.1	139		139	
or							
Strawberries	5.1	6.0	37.3	48.4		48.4	
Raspberries	3.4		42.3	46		46	
Blackberries (3 h. tbsp., no sugar)	5.3	9.3	44.7	59		59	
Two eggs, any form except fried*	54.2	111.6		166		166	
Bread—one slice, thin toasted, white or whole wheat	11.3	3.6	65.3	80			80
Butter, one pat, 15 grams	0.6	118.6		119			119
Beverages, one glass whole milk	29.8	81.8	45.1	157		157	
or							
One cup of coffee or tea (¼ cup of milk, 1 tbsp. cream, 2 cubes sug.)	11.5	71.7	73.1	156			
Totals—Averages	95	315	205	615		418	199

*One of the eggs may be exchanged for 3 Domino lumps or 2 heaping teaspoons of sugar, which may be used in coffee or tea or on berries or grapefruit.

Two eggs and glass of milk may be exchanged for one shredded wheat biscuit or five tablespoons of puffed rice with cream and part of above sugar.

Lunch

	PROTEIN	FAT	CARBOHYDRATES	CALORIES	URIC ACID GRAMS	PROTECTIVE	NONPROTECTIVE
Vegetables, cooked, choice of any three							
Beets, 2 h. tbsp.	6.6	0.7	21.2	29	trace	29	
Carrots, 3 h. tbsp.	2.2	1.6	13.9	18		18	
Onions, 1 whole	4.9	16.7	20.1	42		42	
String beans, 2 h. tbsp.	2.0	6.1	4.7	13	0.006	13	
Spinach, 2 h. tbsp.	8.6	38.1	10.7	57	0.072	57	
Asparagus, 3 stalks, about 125 grams.	7.7	1.2	14.4	23	0.024	23	
Cauliflower, 2 h. tbsp.	4.4	1.1	2.0	8	0.024	8	
Vegetables, raw, choice of any three. May be prepared as salad with lemon juice.							
Lettuce (¼ average head)	2.3		5.7	9	0.009	9	
Tomato (Group II, med. size.)	9.8	3.7	32.8	46		46	
Celery (3 small stalks)	2.1	0.5	5.9	8	0.015	8	
Endive (4 stalks)	2.0		5.0	7	trace	7	
Water cress (3 h. tbsp.)	1.4	1.0	7.4	9.8	trace	9.8	
Cheese, choice of one of the following: Cottage, Edam (Group III), Swiss (average helping), Roquefort (about 20 grams)	27 Average	51 Average	2 Average	80 Average			80
Two Saltines	2.6	7.0	16.8	26			26
Bread, one slice as in breakfast	11.3	3.6	65.3	80			80
Butter, one pat, 15 grams	0.6	118.6		119			119
Beverages							
One glass whole milk	29.8	81.8	45.1	157		157	
or							
One glass buttermilk	26.8	10.1	42.9	80		80	
Totals—Averages	90	260	200	550	0.025	300	305

Option: Plain fresh fruit salad, no sugar or dressing, or with 2 tbsp. French dressing, or 1 tbsp. dressing half mayonnaise and half whipped cream instead of Group I.

DINNER OR SUPPER

	PROTEIN	FAT	CARBOHYDRATES	CALORIES	URIC ACID	PROTECTIVE	NONPROTECTIVE
Soup—Vegetable, prepared without meat stock. Except potatoes or lima beans, 4 oz., or	14.3		2.5	17			
Six oysters, raw. No condiments except lemon juice	21.6	9.5	12.9	44	0.087		44
Meats, fish or fowl. Choice of one only							
Beef, well done, sirloin, 1 slice, lean 100 grams.	95.7	15.4		111	0.111		111
Mutton leg, 1 slice, 75 grams.	76.9	157.6		234	0.078		234
Lamb chop, 1 chop, 100 grams.	89	278.1		367	0.114		367
Fish (Perch, Sole, Trout, Bass, Cod — Any way except fried — About 100 grams) — Average	85	5	7	97	0.130 0.130 0.168 0.130 0.114		97
Chicken, roast, 1 slice, 100 grams	131.6	40.9	8.6	181	0.087		181
Vegetables, raw, choice of any three. May be prepared as salad with lemon juice							
Lettuce	2.3		5.7	9.0	0.009	9.0	
Tomato	9.8	3.7	32.8	46		46.0	
Celery	2.1	0.5	5.9	8.0	0.015	8.0	
Endive	2.0		5.0	7.0	trace	7.0	
Water cress	1.4	1.0	7.4	9.8	trace	9.8	
Vegetables, cooked, choice of any three							
Beets, 2 h. tbsp.	6.6	0.7	21.2	29	trace	29	
Carrots, 3 h. tbsp.	2.2	1.6	13.9	18		18	
Onions, one whole	4.9	16.7	20.1	42		42	
String bean, 2 h. tbsp.	2.0	6.1	4.7	13	0.006	13	
Spinach, 2 h. tbsp.	8.6	38.1	10.7	57	0.072	57	
Asparagus, 3 stalks	7.7	1.2	14.4	23	0.024	23	
Cauliflower, 2 h. tbsp.	4.4	1.1	2.0	8	0.024	8	
Fresh fruit salad—no sugar or dressing, 4 heaping tbsp. Fruits in season	2.0	8.0	120.0	130		130	
Bread, one slice, as in breakfast. No butter	11.3	3.6	65.3	80			80
Beverages:							
One glass whole milk or	29.8	81.8	45.1	157		157	
buttermilk	26.9	10.1	42.9	80		80	
Totals	175	290	310	775	0.114	430	225
Totals for entire three meals	360	865	715	1940	0.139	1180	760

THE BASIC DIET AS PRESENTED TO PATIENTS

Breakfast—

Choice of one of the following fruits:

One orange, sliced or as orange juice (no sugar)

One-half grapefruit (no sugar)

Strawberries, raspberries, blackberries (3 heaping tablespoonfuls, no sugar)

Two eggs, any form, except fried[1]

One slice of thin whole wheat or white bread (toasted)

Butter, one pat (15 grams)

Beverages, one glass of whole milk[2] or one cup of coffee or tea (¼ cup of milk. 1 tbsp. cream, 2 cubes sugar)

[1]One of the eggs may be exchanged for three Domino lumps or two heaping teaspoons of sugar, which may be used in coffee or tea or on berries or grapefruit.

[2]Two eggs and glass of milk may be exchanged for one shredded wheat biscuit or five tablespoons puffed rice with cream and part of above sugar.

Lunch—

Vegetables, cooked.[1] Choice of any three of the following:

Beets, 2 heaping tbsp.; carrots, 3 heaping tbsp.; onions, one whole; string beans, 3 heaping tbsp.; spinach, 2 heaping tbsp.; asparagus, 3 stalks (about 125 grams); cauliflower, 2 heaping tbsp.

Vegetables, raw. Choice of any three of the following (may be prepared as salad with lemon juice):

Lettuce, ¼ average head, 1 medium-sized tomato, 3 small stalks of celery, 4 stalks of endive, 3 heaping tbsp. water cress

Cheese, choice of one of the following:

Cottage, Edam, Swiss, Roquefort (average helping, about 20 grams). Two saltines

One slice of white or whole-wheat bread (toasted)

Butter, one pat (15 grams)

Beverages, one glass of whole milk or one glass of buttermilk

Dinner or Supper—

Soup, vegetable, prepared without meat stock, except potatoes or lima beans (4 oz.) or 6 oysters, raw. No condiments except lemon juice

Meats, fish or fowl: Choice of one only

Chicken, 1 slice (100 grams)

Lamb chop, 1 chop (100 grams)

Mutton leg, 1 slice (70 grams)

Beef, sirloin, 1 slice, lean (100 grams)

Fish: perch, sole, trout, bass, cod (any way except fried, about 100 grams)

Vegetables, cooked. Choice of any three:

Beets, 2 heaping tbsp. Carrots, 3 heaping tbsp. Onions, one whole. String beans, 2 heaping tbsp. Spinach, 2 heaping tbsp. Asparagus, 3 stalks. Cauliflower, 2 heaping tbsp.

Vegetables, raw. Choice of any three of the following:

May be prepared as salad with lemon juice.

Lettuce, ¼ average head. One medium-sized tomato; 3 small stalks of celery; 4 stalks endive; water cress, 3 heaping tbsp.

Fresh fruit salad (no sugar or dressing), 4 heaping tbsp. (Fruits in season)

Bread, one slice, as in breakfast. No butter

Beverages: One glass whole milk or one glass of buttermilk

Avoid.—Preserved, canned, spiced, salted, smoked, or corned meats or fish; pork, tongue, goose, duck, turkey, kidneys, stews, salmon, mackerel, herring, shell fish, liver, sweetbreads, tripe, and fat meats.

Peppers, garlic, spices, gravies. Highly seasoned sauces, mustard, tobasco, paprika, horse-radish, parsnips.

Nuts, preserved, sweetened, syrupy fruits. Pastry, pies, confections, sugar, jellies, jams, preserves, ice cream, pudding, custard. Hot rolls, hot biscuits, hot bread, corn bread, bran. Meat extract soup and bouillons.

All alcoholic or malt drinks.

General Comments and Directions.—Drink water freely between meals, a minimum of ten glasses per day.

Meats and fish allowed only once every other day. Eat only foods prescribed, none others allowed. Be moderate in size of portions.

Remember this diet is elastic and will be amended as the progress of the case indicates. Progress will be determined by the general condition, weight and blood chemistry.

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[1]Option: Plain fresh fruit salad, no sugar or dressing, or 1 tablespoon dressing ½ mayonnaise, ½ whipped cream instead of cooked vegetables.

SUMMARY

1. Chronic arthritis is becoming increasingly important to the medical profession because of its growing social and economic significance.

2. The prognosis of chronic arthritis is good in a large percentage of cases, when treated by men who take a special and keen interest in the disease and are willing to treat it with great patience, zeal and perseverance.

3. No single type of therapy is efficacious in the treatment of all forms of chronic arthritis. All the etiologic possibilities must be most carefully searched for and eradicated in so far as possible.

4. The regulation of diet is of utmost importance in the treatment of chronic arthritis.

5. Each patient should be placed, for a short period, at the beginning of treatment on a basic diet which is then regulated and adjusted to fill the individual requirements of the case. The regulation of the diet depends largely on such factors as the patient's general condition, weight, blood chemistry and clinical progress.

6. The Basic Diet must have the following characteristics:
   a. Low caloric value.
   b. Low carbohydrate, protein and purin values.
   c. Adequate vitamin content.
   d. Elasticity.
   e. Availability.

7. A Basic Diet for chronic arthritis is presented.

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THE USE OF DRUGS IN THE TREATMENT OF ATROPHIC ARTHRITIS*

By A. G. Young, M.D., Boston, Mass.

IN A DISCUSSION of the use of drugs in the treatment of arthritis, one is impressed with the fact that most patients suffering from this disease have been the victims of drug treatment rather than the beneficiaries. Perhaps this is due to the lack of information regarding the etiology, pathogenesis and therapeutics of arthritis. One must also consider the fact that any chronic, painful disease usually places the patient at the mercy of analgesic therapy. Relief from pain is greatly appreciated by the patient and as a consequence analgesia has superseded the search for the etiology and curative treatment of the disease in the minds of many physicians.

Arthritis is one of the oldest diseases known. Sir Armand Ruffer reported lesions of hypertrophic and atrophic arthritis in the remains of Egyptian and Nubian mummies, dating from the period of about 8000 B.C. Despite the antiquity of the disease and its painful and debilitating nature, very little progress has been made as regards its etiology, pathogenesis or treatment. For years arthritis was not distinguished from rheumatic fever and gonorrheal arthritis. This led to many systems of classification which were largely of a clinical descriptive nature and resulted in a confusion of terms which made it impossible to understand an article unless careful clinical histories were presented to explain the nomenclature used. The medical profession at large has considered chronic arthritis as an incurable disease which could be controlled somewhat by analgesic drugs. Empirical treatments of every description have been advocated by medical and nonmedical men, frequently leaving the patient a victim of neglect and quackery. Within the past two decades rheumatic fever and arthritis have received the serious study of a number of investigators who have gradually presented fundamental studies which form a foundation on which a more thorough understanding of these diseases can be based. As a result of these studies, a more rational therapeusis has evolved, which, although far from attaining perfection, has shown the fallacy of certain measures and the value of those methods of treatment which are directed toward elimination of the cause of the disease and the restoration of the disturbed physiologic processes.

In order to discuss the rationale of the therapeutic measures which are used it is necessary to briefly review the clinical course of atrophic (including infectious) arthritis.† The rôle of foci of infection as etiologic factors was stressed by Billings[1] and the systemic nature of the disease has been pointed out by numerous writers.

*From the Robt. B. Brigham Hospital.

†At a meeting of the American Committee on Rheumatism in Philadelphia, March 17, 1928, chronic arthritis was divided into two main types, the atrophic and hypertrophic. The atrophic group includes the infectious arthritis.

The onset of atrophic arthritis may be acute or insidious. In those patients with an acute onset marked by a febrile reaction there is usually a focus of infection or a history of a recent infectious disease. The joints show the cardinal signs of inflammation and there may be muscle pains also. There is usually a mild leucocytosis. The chief complaint is pain and stiffness of the joints and a sense of extreme fatigue. The condition may subside within a few days to a few weeks or may pass into a chronic state. The pain is not always comparable to the degree of swelling, but usually there is direct relationship between the two. In the chronic state the disease may continue to be marked by continuous or intermittent swelling of the joints but without loss of weight or general debility. The soft tissues about the joints are swollen and there may be an accumulation of fluid within the joint. The joint space, cartilage and bone give a normal appearance. There is usually a mild secondary anemia, with or without a leucocytosis. However, if the patient becomes "atrophic" a general systemic reaction occurs marked by: loss of weight, a mild anemia, a lowered systolic blood pressure and mild tachycardia; atrophy of the muscles (especially those about the affected parts) and atrophy and spindling of the shafts of the bones, with a softening and distortion of the ends. There is narrowing of the joint space and a loss of interarticular cartilage. The palms of the hands and soles of the feet are usually cold and sweat profusely. The nails become hard, brittle and ridged. Later they may drop off. The skin becomes dry, glistening and parchment-like, showing that the peripheral circulation has been greatly diminished. This can be verified by the use of the capillary microscope. The posture of the patient is poor. Gastrointestinal disturbances, especially constipation, are common. The affected joints usually become fixed in a flexed position due to the fact that the patient holds them in that position because it is the least painful. Later, distortion may take place, due to muscle spasm, which is so severe that dislocations occur. The basal metabolism is slightly lowered in most of these patients.[2] There is a mild anemia, frequently characterized by a low hemoglobin and a normal red cell count. Constipation is usually marked, associated with diarrhea, visceroptosis, etc. This résumé of the general condition is only an attempt to point out the major and most common signs and symptoms in order to more intelligently discuss the use of the various therapeutic measures employed.

THE DRUGS USED IN THE TREATMENT OF ARTHRITIS

The drugs used can best be classified according to their effect on the patient.

1. Analgesics
   - Salicylates
   - Cinchophen
   - Acetanilid and phenacetin
2. Drugs used for their effect on the circulation
   - Digitalis
   - Nitrites
   - O-Iodoxybenzoic acid
3. Drugs used for their specific action
   - Autogenous vaccines
   - Emetine

4. Drugs used for their nonspecific action
   - Foreign protein
   - Milk
   - Iodides
5. Tonics
   - Arsenic
   - Strychnine
6. Drugs used for their nutritional value
   - Vitamins
   - Calcium
7. Laxatives

In the above classification, one notices that most of the analgesics also fall under the second heading. This is explained by the fact that most of them are also diaphoretic and therefore increase the peripheral circulation. However, this action is of short duration and cannot be depended upon.

I. Analgesics

Salicylic Acid and Its Derivatives

(C_6H_4 . COOH . OH)

Under this heading the salicylates undoubtedly rank first. (However, Hanzlik[3] says that cinchophen has an identical action.) The free acid is irritating causing nausea and vomiting when given internally. For this reason the salts are used. The acid has some antiseptic properties but the salts are practically devoid of this action.

Absorption.—

Cutaneous.—In fatty and alcoholic solutions, salicylic acid and its esters are readily absorbed from the intact skin (Hanzlik[3]). Bourget[4] found that lard or lanolin was the best vehicle for absorption.

Gastrointestinal.—The soluble salts are slowly absorbed in the stomach while the insoluble salts pass into the intestine, where they are rendered soluble before absorption occurs.

Distribution.—

After absorption salicyl is found in practically every secretion, fluid and organ of the body (Hanzlik[3]). Scott, Thoburn and Hanzlik[5] compared the salicyl content of the blood and joint fluid of patients suffering from rheumatic fever. There was slightly more salicyl in the blood than in the joint fluid. Apparently there is no selectivity of salicyl for the inflamed joints.

Excretion.—

Salicylates are excreted in the urine mainly as such (Hanzlik[3]). The rate of elimination depends upon the condition of the patient and the type of compound used. Hanzlik, and his collaborators[6, 7] report a median duration of seventy-eight hours in normal subjects, seventy-two hours in rheumatic patients, and of eighty hours in patients with miscellaneous conditions. In regard to the type of compound it was found that the salicyl derivatives require a much longer period for complete excretion than the sodium salt. In rheumatic fever the total excretion was found to be 15 to 20 per cent less than in normal individuals. They believe this to be due to increased destruction of the salicyl in the rheumatic patient.

Action.—

Local.—Salicylic acid is an irritant and dissolves the epithelial cells. This irritant action also prevents its use internally since it causes nausea, vomiting, and diarrhea. Sodium bicarbonate is prescribed with sodium salicylate to prevent the precipitation of free salicylic acid.

Emetic Action.—Emesis can be produced with any of the salicylates, regardless of the mode of administration, if sufficient dosage is given since this action is due to a central effect as demonstrated by Eggleston and Hatcher.[8]

Kidney.—Therapeutic and toxic doses of salicylates affect the kidney as shown by increased permeability to uric acid (and possibly other metabolites), the production of albuminuria, the changes in urinary output and renal function. Hanzlik and his collaborators[9, 10, 11] have shown diminution in renal function and the production of albuminuria of renal origin in rheumatic and nonrheumatic patients following therapeutic doses of salicylates.

Circulation.—All concentrations of salicylates tend to relax the blood vessels in perfused animals. In therapeutic doses the circulatory effects are probably secondary to the antipyretic and diaphoretic action which appears to be of central origin as is also the analgesic action.

Respiration.—Respiration is not affected by ordinary doses but full therapeutic doses depress and quicken it.

Ear.—The tinnitus aurium, characteristic of cinchonism, occurs after full therapeutic doses of salicylates. The susceptibility varies with the individual but this symptom is usually a good indication to stop administration of the drug.

Metabolism.—(a) Nitrogen: The excretion of nitrogen is generally increased as shown by Denis and Means[51] on normal subjects taking a known diet. The patients received up to 6.6 gm. of salicylates daily and showed an increased excretion of nitrogen, also an increase in the phosphates and uric acid.

(b) Sulphur: Baumann and Herter[12] showed an increase in sulphate excretion. This was confirmed by Kumagawa.[13]

Diaphoresis Temperature and Heat Regulation.—Sweating usually occurs after therapeutic doses of salicylates. It is usually more profuse in febrile conditions, sometimes becoming so severe as to produce a state of exhaustion. The mechanism is imperfectly understood but Hanzlik suggests that it is associated with the vasodilator action (central) which is so important a factor in its producing antipyresis.

Effect upon Immune Bodies.—Swift[14, 15] gave daily doses of sodium salicylate orally to rabbits that had been injected intravenously with living and dead Streptococcus viridans cultures and with washed sheep red blood cells. He found that the animals receiving the salicylate suffered a decrease in the formation of antibodies, agglutinin, hemolysin and complement fixation. Also he found that the rabbits receiving intravenous injection of antigens which had been previously treated in vitro with sodium salicylate showed lower antibody curves than did the rabbits receiving untreated antigen intravenously and salicylate gastrically.

Toxicity.—

The symptoms are characterized by nausea, vertigo, ringing in the ears, headache, vomiting, and occasionally diarrhea.

The postmortem changes consist of destruction of erythrocytes, congestion of most viscera, necrosis of the spleen, lymphoid elements, and nephritis. The lethal dose in man is about 1 gram per kilo.

Idiosyncrasy.—

The acetyl derivative provokes hypersensitive reactions more frequently than the other derivatives. The reaction appears to be similar to allergic conditions and is marked by increased capillary permeability. The symptoms are: constriction and edema in the throat with dysphagia and salivation,[16] congestion in the nose, swelling of the eyelids, and edema of the pharynx.[17, 18, 19]

Salicyl edema has been described by Hanzlik and his collaborators,[7] who believe it is due to disturbed renal function.

Cinchophen

Chemically cinchophen or atophan is phenylcinchoninic acid. Its formula is $[C_6H_5.C_9H_5N.(COOH)]$. It is quite insoluble but the sodium salt is soluble and nonirritant. Its chief clinical derivative is the ethyl-ester of methyl phenylcinchoninic acid ($CH_3.C_9H_4N.C_6H_5COOC_2H_5$). It is known as "neocinchophen," "tolysin" and "novatophan." It is not readily soluble in water, acids, or alkalies but is very soluble in the lipoid solvents.

Pharmacologically, Hanzlik[3] says that the action of cinchophen is exactly the same as that described for salicylates in so far as the cinchophen actions have been studied. It is certain that its toxic and clinical actions are practically indistinguishable from the salicylates. Therefore, it is obviously unnecessary to repeat the information just detailed for the salicylates.

Methods of Administration.—

Oral.—This is the chief route of administration of cinchophen and the salicylates since practically all of the compounds are readily absorbed when introduced into the gastrointestinal tract. Nausea from gastric irritation can be reduced by administering sodium bicarbonate with the salicylates or cinchophen but the nausea due to large or repeated doses is central and therefore cannot be avoided by other routes of administration.

Rectal.—This method is sometimes advantageous when the patient is suffering from nausea due to other causes than the drug. Heyn[20] recommends it highly. The first adult dose consists of 8 to 10 gm. of sodium salicylate in 120 to 180 c.c. of plain or starch water. If no symptoms of intolerance appear it may be repeated in twelve hours.

Intravenous.—There is no advantage to be gained by the intravenous administration of either salicylates or cinchophen. Conversely this method does predispose the patient to reactions and according to Hanzlik[3] can cause considerable harm to the heart and other organs and may cause collapse. For this reason this method is mentioned only to point out its lack of value and possible danger.

Clinical Considerations.—

In administering salicylates or cinchophen to an arthritic patient, one can depend only upon their properties of analgesia and antipyresis; since there is no evidence to prove that these substances have any curative properties and there is considerable evidence to prove that they are devoid of any such action. Thus Swift[21] showed that salicylates decrease the properties of the blood for specific antibody formation. Miller[22] showed that the prophylactic administration of salicyl did not protect rabbits against arthritis produced by intravenous injection of hemolytic streptococci. Davis[23] found the rabbits with streptococcal arthritis that were treated with salicylates frequently died sooner than the controls. Swift and Boots[24] had a similar experience in that the salicylates appeared to produce an exacerbation of the infection and the cardiac lesions were not influenced. They concluded that the earlier death in the treated rabbits was due to the combined bacterial action on the kidney and the nephrotoxic effects of the salicylates.

These experiments and others led Hanzlik[3] to conclude that: "the antichemotic actions of cinchophen and salicyl are variable and undependable, and, when obtained they probably occur at the expense of circulatory depression."

It is not the purpose of this paper to discuss the action of these substances in rheumatic fever, however, there is a close analogy to be drawn.

In conclusion one may say that cinchophen and salicylates are efficient analgesics and antipyetics. In administering them to arthritic patients one can relieve the pain and muscle spasm, thereby permitting the patient to relax and rest; these are very important objectives to be obtained, but no permanent relief should be expected from such measures.

Anilin Derivatives

The anilin derivatives, acetanilid ($C_6H_5.NHCH_3CO_2$), and phenacetin ($C_2H_5.O.C_6H_4.NH.CH_3CO$) are two of the most powerful analgesics and antipyretics known. However, they exhibit in a milder degree the toxic actions of anilin such as destruction of the red blood corpuscles, methemoglobenemia and the production of severe cardiac lesions especially of the conduction mechanism of the heart.[25, 26]

Phenacetin is less toxic than acetanilid and may be used occasionally in five or ten grain doses without injury, but in a chronic condition such as arthritis it should only be prescribed when other analgesics have become intolerable.

Morphine and Codeine

One is seldom justified in administering morphine to an arthritic patient. It is a dangerous procedure to start since the patient, even in the acute stage, usually suffers pain for a sufficient period of time to develop a morphine habit.

Codeine is not so prone to produce a habit but is usually not as efficient as salicylates or cinchophen in relieving the pain. Therefore, one should use narcotics in arthritis only under very unusual circumstances, thereby avoiding the possibility of starting a habit which will only add to the patient's discomfort and physical injury.

II. Drugs Used for Their Effect on the Circulation

As has previously been mentioned the circulation of the patient with arthritis is very noticeably disturbed. This is a prominent clinical symptom as shown by a mild hypotension and tachycardia, with mild to severe trophic disturbances due to depression of the peripheral capillary circulation. Boas and Rifkin[27] and McCrae[28] have pointed out the incidence of cardiac lesions in arthritis deformans. The work of Rowntree and Adson[29] has shown that surgical release of the sympathetic control to the part is followed by noticeable symptomatic improvement.

Digitalis

The knowledge of the pharmacology and uses of digitalis is so universally disseminated that it would be superfluous to repeat it here. Pemberton[30] recommends the administration of daily doses of 9 to 15 minims of the tincture to improve the circulation. The rational of this treatment is not clear, since there is no evidence to show that the heart is ordinarily involved in arthritis. It is definitely known that digitalis does not affect the normal heart unless given in toxic doses. Therefore, its value in the treatment of arthritis, not complicated with heart disease, is questionable. Where definite cardiac signs or symptoms are present larger doses should be given.

Nitrites

Nitrites reduce the tone of the arterial musculature, thereby producing an immediate fall of blood pressure due to vasodilatation. This effect is particularly noticed in the vessels of the skin. The action appears soon (one to five minutes) after administration and disappears within five to fifteen minutes.

Pierce and Pemberton[30] administered doses of $\frac{1}{12}$ to $\frac{1}{4}$ grains of erythroltetranitrate to a selected group of patients. They obtained a "favorable influence" in 12 out of 32 cases treated.

Possibly this is a step in the right direction but due to the fact that nitrites produce methemoglobinemia if given over an extended period, and also the fact that the vasodilatation is brought about at the expense of a lowered blood pressure it would appear that nitrites are not the ideal vasodilators for the treatment of arthritis.

O-Iodoxybenzoic Acid: "Amiodoxyl Benzoate." (N.N.R.)

Chemically this substance has the formula ($C_6H_4.COOH.IO_2$). The ammonium salt was officially called amidoxyl benzoate by the Council on Pharmacy and Chemistry. It was introduced as a therapeutic agent for arthritis by Young and Youmans[31] in 1926.

Phamacology.—

Local.—The free acid and its salts are nonirritant to the unbroken skin, but when injected hypodermically, a red area appears associated with a stinging, burning sensation. This persists for a short time and is not followed by a slough. When applied to the mucous membranes it acts as an oxidizing agent and is effective in the treatment of Vincent's angina. The pure ammonium salt will not injure the mucous membranes. It is antiseptic especially for staphylococci and streptococci and the colon typhoid group.

Heart and Circulation.—

Heart.—In the perfused heart Loevenhart and Eyester[32] found that sodium iodoxybenzoate produces rigor. They say: "The power to cause the heart to develop rigor is apparently due to the power to oxidize something in the heart muscle." The substance would not replace molecular oxygen in the perfused heart.

Circulation.—Experimentally, Loevenhart and Grove[33] found an occasional slight fall in blood pressure, with an increase in cardiac output. They made the very interesting observation that: "Cardioplethysmographic tracings showed that the fall of blood pressure is not due to any cardiac effect of the drug. Perfusion of the isolated intestines proved that the salt does not act directly on the vessel wall" and . . . . concluded that the fall in blood pressure is due to depression of the vasomotor center. This is further substantiated by observations on the capillary flow of the nail bed which is greatly increased as is also the lymph flow. The author found that the lymph flow from the thoracic duct of a fasting dog was increased four to five times by the injection of 4 c.c. of a 1 per cent solution of the ammonium salt.

Blood.—

Sodium iodoxybenzoate oxidizes hemoglobin to oxyhemoglobin (Loevenhart and Grove).

Effect on Immunologic Reactions.—

Arkin[34] found that sodium iodoxybenzoate stimulates phagocytosis of streptococci and staphylococci by human leucocytes. He attributed this to an activation of the opsonin by the "oxygen containing substance," since a substance which liberates oxygen readily stimulates phagocytosis.

Hektoen[35] found that this substance stimulates the production of specific hemolysins in dogs. Arkin[36] repeated this work on rabbits and obtained the same results. He also obtained an increase in the production of specific agglutinins in rabbits immunized with killed typhoid bacilli. He suggests that these results are due to an acceleration of the oxidation in the tissues which are the site of antibody formation.

Effect Upon Allergic Reactions.—

Amberg and Knox[37] studied the effect of sodium iodoxybenzoate in allergic reactions and found that while it did not influence the general allergic reaction it did prevent the local reaction such as one sees in the tuberculin test.

It was also shown that intravenous injection of this compound inhibits the inflammatory reaction produced by mustard oil. They, therefore, concluded that the action is an antiinflammatory reaction or an antichemosis. Arkin[36] showed that tuberculin is oxidized by the drug in vitro.

Respiration.—

Therapeutic doses do not affect the respiration but in toxic amounts a temporary apnea is produced.

Fate and Excretion.—

The salts of o-iodoxybenzoic acid are reduced to o-iodobenzoic acid and excreted largely in the urine as o-iodohippuric acid. These experiments were

performed on patients and although the results were not satisfactory from a quantitative standpoint they coincide with the work of Novello, Miriam and Sherwin[38] who fed o-iodobenzoic acid to dogs and found it to be excreted in the urine partly unchanged, but mostly as o-iodo-hippuric acid. The distribution in the tissues has not been determined. It is important to state here that o-iodoxybenzoic acid *does not break down in the body or test tube to yield iodides or salicylates.*

Toxicity.—

The toxicity of the pure salt depends more upon the rate of injection than upon the amount given. In experimental animals death is usually of a respiratory nature but may be circulatory due to heart rigor.

Postmortem findings are largely negative. The most consistent finding is congestion of the lung bases. Chronic poisoning has never been produced in animals nor has it been seen in patients.

A death has been reported by Manace[39] and I have been informed of another death but in this latter instance the drug was submitted to a pharmacologist who found that "it contained some very toxic ingredient aside from the ammonium salt of iodoxybenzoic acid."

Reactions.—

In an acute or subacute condition the administration of the drug will usually provoke a febrile reaction which lasts for from one-half to two hours. In chronic patients the administration is marked by a stinging sensation of the mucosa of the nose and mouth, the face becomes flushed, the patient usually salivates and may become nauseated. There may be a sensation of substernal oppression. A tingling sensation is noticed in the extremities. This reaction usually subsides within ten to forty-five minutes after the administration of the drug. In some patients the nausea persists for a longer period, vomiting may occur and occasionally a mild diarrhea. The author has never experienced a fatality or a reaction of alarming proportions which could be attributed to the drug.

Repeated examinations of patients treated over a long period of time have failed to show evidence of nephritis.

Administration.—

(a) *Intravenous.*—This method was recommended by Young and Youmans[31] in their first report and has proved to give the most satisfactory results. One gram of the ammonium salt is dissolved in 100 c.c. of sterile salt solution and given by gravity method over a period of ten to fifteen minutes. To avoid too rapid flow into the vein it is well to use a small needle (about 22 gauge) and elevate the gravity set about four feet above the patient's arm. If this method is followed, *using a pure product and rubber tubing that has been thoroughly cleansed,* alarming reactions will not occur.

(b) *Rectal.*—Smith[40] reported favorable results when the drug was given in the form of a retention enema. He used 1.5 to 2 gm. in 200 c.c. of normal saline. A cleansing enema should precede the administration of the drug by two hours. This method is advantageous and usually effective in patients who are not suitable for intravenous therapy.

(c) *Oral.*—The drug has been given orally in the form of the calcium salt in capsules. The insolubility of the calcium salt decreases the irritant action and obviates nausea due to the ammonium ion which is liberated from the ammonium salts. The dose consists of 1.5 to 2 gm. The results obtained are variable. In some patients quite satisfactory results occur; but in a larger percentage it is unsatisfactory.

Clinical Considerations.—

The clinical use of the salts of o-iodoxybenzoic acid is of recent origin and therefore one should be conservative in attempting to evaluate this drug in the treatment of arthritis. However, since the first report by Young and Youmans in 1926, fifteen papers reporting 589 cases have been published. The average improvement reported shows that 66.3 per cent showed marked to moderate improvement, while 23.7 per cent showed slight or no improvement. Of this group, most of the patients were classified as "chronic," "infectious" or "proliferative." The remainder were acute infectious or gonorrheal with a few cases of rheumatic fever and a few hypertrophic arthritides. These figures include the report of Stein and Taube[41] who treated 102 cases (about one-sixth of the patients reported) with no improvement. This report merits especial consideration since it is the only published account of complete failure to obtain improvement with this drug. It is interesting to note that the report included 10 cases of acute infectious arthritis and 2 cases of rheumatic fever. Only the rheumatic fever patients were confined to bed. The authors say: "Any improvement, two weeks after the administration of the drug, we consider not to be due to the drug." Obviously this is not a fair estimate of the value of the drug since as Neighbors[42] remarked in commenting on this same paper: "While it is true that relief of symptoms often begins during treatment, it is a repeated observation that improvement in joint symptoms may not be apparent until a few weeks have elapsed, and an improvement in general health may be still later manifested." Furthermore, it is not consistent with past clinical experience to expect improvement in acute infectious arthritics who are not confined to bed. In the chronic patients, undoubtedly other methods must be combined with the drug treatment in order to obtain improvement. It is pertinent to repeat here the statement made by Young and Youmans[31] in the original report on this drug: "We believe that it will never be possible with a single drug to cure a patient with arthritis who has developed permanent deformity and crippling, and that the proper treatment is a combination of methods, including the use of prophylactic and curative orthopedic procedures, the removal of foci of infection and general hygienic measures as well as drug therapy."

In his first report on this drug following the work of Young and Youmans, Smith[40] pointed out the chemical relationship between o-iodoxybenzoic acid and salicylic acid; i.e., that one is the o-iodoxy- and the other the o-hydroxy-derivative of benzoic acid. He suggested that their actions might be very similar, and stressed the analgesic action of o-iodoxybenzoate. This idea has been accepted by some observers and is quoted by Bartlett[43] and by Pemberton[30] who says that the drug is "a glorified salicylate." The error of this conclusion is readily demonstrated by the fact that o-iodoxybenzoate acts in

the body by virtue of its available oxygen attached to the iodin. This was demonstrated by Loevenhart and Grove,[33] and Loevenhart and Eyester[32] and has since been confirmed by me when I recovered the drug from the urine in the form of o-iodo-hippuric acid. Salicylic acid has no available oxygen in its molecule. Further evidence of the difference in action of the two compounds is shown by the fact that o-iodoxybenzoate increases phagocytosis, the formation of specific hemolysins and agglutinins and definitely depresses the sympathetics. Salicylic acid inhibits the formation of specific antibodies and does not affect the sympathetics in ordinary dosage. The salicylates act chiefly by virtue of their analgesic and antipyretic properties; whereas, o-iodoxybenzoates act by virtue of their oxidizing properties which bring about a depression of the sympathetics thereby increasing the peripheral capillary and lymph flow. They are also antiinflammatory agents by virtue of their antichemotic action.[37]

In a later report Smith[44] concluded that patients who are suffering from gastrointestinal disturbances did not respond to treatment with o-iodoxybenzoate. The author cannot agree with these findings, since most chronic arthritics are constipated and a large percentage have responded to this treatment. Certainly patients are encountered who are not improved by the use of this drug, but in my experience these patients have not shown a higher percentage of gastrointestinal disturbance than usual. At present there is no plausable explanation which will cover the entire group.

III. Drugs Used for Their Specific Action

Autogenous Vaccines

The use of vaccines made from cultures of diseased tonsils, teeth, etc., has been practiced for several years. Frequently good results are reported. However, it is very difficult to ascertain to what extent the vaccine acts by virtue of its specific influence and to what extent it may be due to a foreign protein reaction. There is also the difficulty of definitely proving that the organism removed from the tonsils, teeth, etc., was responsible for the arthritis. On the whole, the results have not been sufficiently encouraging to warrant general use. Further development of the work of Small[45] and Cecil, Nicholls and Stainsby[46] may contribute more valuable biologic agents than we have at present.

The vaccine is administered intramuscularly, usually in increasing doses. Beginning with a dose of 10,000,000 organisms it is gradually increased to 75,000,000 or more. Febrile reactions are not uncommon and may be of therapeutic value. The patients frequently complain of increased joint pain during the treatment.

Emetine

Ely[47] and his collaborators have advanced the idea that hypertrophic arthritis is due to Entameba histolytica which enters the body through root infections of the teeth and passes from there to the marrow spaces. Barrow and Armstrong[48] report finding the organism frequently in the stools of arthritis patients.

As a consequence ipecac and its alkaloids have been used by mouth and hypodermically. Up to the present time no work has been done to confirm the findings of Ely and therefore it is not possible to evaluate this treatment.

IV. Drugs Used for Their Nonspecific Action

Under this heading come typhoid vaccine, "mixed cultures," milk, and some colloidal compounds which are capable of producing a febrile reaction. All of these substances are dependent upon the production of a febrile reaction for their therapeutic results. Typhoid vaccine is one of the most commonly used agents. It is injected intravenously in doses varying from 15,000,000 to 175,000,000 dead typhoid organisms. Within one-half hour to two or three hours the patient experiences a chill and fever associated with headache, malaise, nausea, and sometimes vomiting. This is followed by profuse sweating and a gradual return of the temperature to normal. The duration of the reaction as well as its severity depends upon the number of dead organisms in the dose given. It frequently lasts twenty-four to thirty-six hours after which the patient may experience a pronounced relief from pain and stiffness. These treatments are usually given at three to seven day intervals, sometimes with increasing doses. The effect produced from an immunologic viewpoint and its value is difficult to determine. However, it is definitely known that during the period of the "chill" when the temperature is rising, there is a profound depression in the rate and volume of the capillary circulation to the skin. At this time the patient is the most uncomfortable and may complain of increased joint pain. Following this period when sweating begins, the capillary circulation to the periphery is greatly increased in rate and volume and this is associated with relief from pain. This effect persists for about twenty-four hours after the fever has subsided and the joint improvement persists for a longer time. In some instances this is sufficient to restore the physiologic function of the joint circulation until the body recovers sufficiently to carry on the normal circulation.

One should bear in mind that this procedure is "shock therapy" and in large doses as 125,000,000 dead organisms there is danger of severe reactions and even death. Histologically, amyloid disease may be produced in experimental animals. I have seen thrombosis of the vessels of the feet and legs so severe as to cause gangrene and necessitate a bilateral amputation, following large intravenous doses of dead typhoid bacilli. Severe atrophic arthritics are frequently unable to withstand shock therapy.

Iodides

Since the action of iodine is not definitely known its use (largely as potassium iodide) must be considered to be empirical. Pemberton[30] suggests that its action is due to its influence on the thyroid gland. It is usually described as an "alterative." Regardless of what action the iodides may have, they have proved to be valuable therapeutic adjuncts, when combined with other measures.

When given by mouth they are expectorants and may produce emesis. They are readily soluble and are absorbed rapidly. For this reason *there is nothing to be gained by intravenous injections which may be followed by severe edema.*

Endocrine Substances

Since there is no definite information on which to base an opinion as to the rôle played by the endocrines in arthritis, it is difficult to evaluate or explain the use of the endocrine extracts in this condition.

Thyroid.—

Thyroid in the form of whole dried gland has been used extensively in doses of from 5 to 15 gr. daily until the pulse rate or nervous condition of the patient indicates that it should be discontinued. Despite the fact that the atrophic arthritic may have a slightly lowered basal metabolism and responds to thyroid medication, one cannot conclude that he is suffering from hypothyroidism. As a matter of fact he is more frequently the *hyper*thyroid type of individual. For this reason, one cannot determine how desiccated thyroid exerts its beneficial action. Improvement may be obtained without changing the basal metabolism. Some patients are definitely intolerant to thyroid medication; therefore, it is advisable to begin with small doses (½ to 1 grain, t.i.d.), which may be gradually increased.

Ovarian Extracts.—

Since arthritis frequently manifests itself during the menopause, considerable attention has been given to the relation of the ovaries to arthritis in women. At the present time no definite information is at hand and opinion varies greatly as regards the therapeutic value of ovarian extracts in arthritis occurring at this time.

V. Tonics

Since patients with atrophic arthritis usually suffer from loss of weight, anorexia, severe fatigue and anemia, tonics play an important part in the treatment.

Arsenic

Arsenic has been used for many years either as Fowler's solution by mouth or injected as sodium cacodylate. In either form the benefit gained probably is the result of its action on the blood regeneration elements and upon metabolism.

Iron

The anemia which accompanies arthritis indicates the use of iron. However, one is frequently disappointed in the results obtained. Usually the anemia does not improve until there is definite improvement in the arthritic condition.

Strychnine

This is the only tonic known in the true sense of the word and is valuable in attempting to restore the muscle tone and prevent atrophy. It is prescribed in many ways, but the well-known "I. Q. and S." mixture appears to give good results and has the added advantage of containing iron.

VI. Drugs Used for Their Nutritional Value

Vitamins

The great advances in nutritional chemistry have thrown much light on the action of the vitamins and their influence on health and disease.

Since arthritis is a disease involving the bones and therefore very probably the calcium metabolism, *Vitamins A and D,* in the form of cod liver oil, have been extensively used. The beneficial results are difficult to evaluate, but on the whole one is impressed with the fact that patients receiving cod liver oil maintain their appetite and body weight better than those who do not receive it.

Vitamin B.—

The gastrointestinal disturbances so frequently encountered in arthritis indicate the value of Vitamin B. This has been especially shown by the work of Fletcher and Graham[49] who found a definite loss of tonicity and loss of haustral markings in the colon in atrophic arthritis. Vitamin B may be administered in the form of yeast, or better, the yeast extract described by Wakeman and Osborn,[50] known commercially as "Harris Yeast." The dose is six to nine tablets daily. The yeast extracts obviate the gas which frequently accompanies administration of the yeast itself.

Vitamin C.—

No definite value can be ascribed to Vitamin C in the treatment of arthritis; but since the citrous fruits are recommended because of their value as basic salts, this vitamin is usually consumed in large amounts. Certainly it can do no harm and it may be beneficial as a "blood builder" as shown by its effect in scurvy.

Calcium.—

The patient with arthritis frequently shows a low urinary P_H and a high total titrable acidity. This indicates a disturbed acid-base balance and probably a loss of calcium. Since the urinary reaction can be changed by the administration of basic salts, calcium in the form of its soluble salts (as calcium lactate) is of special value. It is also well to prescribe milk, custards, etc. Calcium administration should be forced until the P_H of the urine is neutral or slightly alkaline.

VII. Laxatives

Most patients with arthritis suffer from constipation and give a history of requiring frequent laxatives. One should attempt to correct the constipation by posture, exercises, diet and proper hygienic measures. However, one frequently finds that some stimulus is necessary to produce a bowel movement.

Of the milder substances, mineral oil and agar are very suitable. For a laxative cascara or phenolphthalein are quite effective and can be given in diminishing doses as the other measures begin to take effect. The greatest problem is to educate the patient to rely on his habits and not on a laxative for his daily evacuations.

DISCUSSION

In presenting this paper it is not with the intention of promulgating the idea that arthritis may be overcome by simply administering a large number of drugs. No other disease requires more painstaking study and individual attention for successful treatment. Each patient is an individual problem worthy of careful study and thought. The disturbed physiology is a predomi-

nating feature. The physician is confronted with the problem of discovering the cause, the present and past exciting factors and what physiologic processes are disturbed. He may then attempt to remove the cause and correct or restore to normal the disturbed physiology. Some of this treatment can be carried out by the intelligent use of drugs. Unfortunately the patient with arthritis has been too frequently the victim of analgesic remedies with no attempt to remove the cause or correct his present disturbed processes. As a result, valuable therapeutic agents have fallen into disrepute and patients have become hopeless invalids who might have been restored to an active life.

When drug treatment is instituted it should be done with the definite purpose of correcting some phase of the patient's illness. In order to do this, one must know his patient clinically and understand the pharmacology of the drug to be used. Drugs used in this manner in conjunction with other methods, as indicated by the condition of the patient, will be of distinct value and contribute toward the improvement which can be obtained in a large percentage of these patients when properly treated.

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THE TREATMENT OF CHRONIC "INFECTIOUS" ARTHRITIS BY SYMPATHETIC GANGLIONECTOMY AND TRUNK RESECTION*

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ASIDE from removal of foci of infection, the major and relatively more successful forms of treatment for chronic "infectious" arthritis are all directed toward (1) increasing the circulation of the joint, (2) increasing the temperature and thus the metabolism of the joint, and (3) increasing oxidation of articular tissue. These are supposed to be the beneficial results of physical means of treatment such as heat and cold, dry and moist applications, diathermy, massage, exercises, and heliotherapy, and also of certain "medical" procedures, such as "fever therapy" and administration of preparations of thyroid gland.

The treatment of certain cases of chronic arthritis by resection of sympathetic ganglions and trunks was instituted by Rowntree and Adson in the hope that this surgical measure might produce an optimal degree of articular circulation in certain joints at least. The details of the technic, the rationale of the procedure, and the results in the first seventeen cases have been given in a series of papers; this paper will give but a survey of the subject.

UNDERLYING PRINCIPLES

Any superiority in results that may come from resection of sympathetic ganglia and trunks, in certain well selected cases of chronic infectious arthritis, may lie solely in the fact that by this procedure the desired beneficent state is maintained over a protracted time, possibly permanently, instead of intermittently for only a few minutes or hours at a time.

The general principle of resection of sympathetic ganglia and trunks is to cut and remove the sympathetic ganglia and their rami that contain vasoconstrictor fibers to the vessels of the extremities, thereby increasing the circulation and temperature of the joints of the extremities, and probably increasing tissue-oxidation in them.

Data are not at hand to support the idea that resection of sympathetic ganglia and trunks corrects a primary "neurogenic" cause for chronic polyarthritis. But in the light of our studies we feel that the neurogenic theory merits further investigation. In 1889 Spender graphically described "the tangled web of strange neurotic things" that comprised at least part of the picture of chronic arthritis. Even before this the old humoral theory of the causation of arthritis had begun to be supplanted by the conceptions of Remak, Charcot, Trousseau, and others in favor of a primary neural genesis. Garrod, although supporting the theory of dystrophy, believed that the associated nervous

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phenomena were secondary rather than primary. After the theory of infection was launched by Schuller, the theory that the disease was neurogenic lost ground until certain clinicians tried to reconcile conflicting views and suggested that infectious trophoneurosis was present.

Several investigators have reported the finding of certain pathologic changes in various portions of the central nervous system in arthritis. In many instances there are strikingly present such clinical phenomena as altered vasomotor tonus, hypotension, pigmentation, cyanosis of the skin over the joints, clamminess, and increased sweating, particularly of the extremities. No one has definitely determined whether they result from some primary and noninfectious disturbance of the central or sympathetic nervous system, or from secondary disturbances arising from the effect on the nervous system of some toxic, bacterial or metabolic insult. The present consensus of opinion is that they are secondary neurogenic phenomena, the sympathetic nervous system participating in a general systemic disturbance, which might well be of infectious origin. Whatever the source, there is evidence that resection of sympathetic ganglia and trunks may restore, to a certain extent, some of these neurogenic alterations, chiefly, however, in the most distal joints of the extremities.

CLASSIFICATION OF CASES

Suitable for Operation.—We have limited use of the operation to cases of chronic infectious arthritis. This term is in general synonymous with the terms atrophic, proliferative, rheumatoid, and periarticular arthritis. It is held to be in contradistinction to osteoarthritis, hypertrophic arthritis and degenerative arthritis. However, we use the term without assuming that our opinion on etiology is final, but we use it in line with the clinical classification of Hench, which is based on presumptive cause, and that is used on the arthritic service of this clinic (Tables I and II).

Operation is indicated probably in only a small percentage of cases of chronic "infectious" arthritis. Satisfactory results have been obtained frequently in cases in which there have been changes in soft tissue of the joints of the hands and the feet. No benefit has been obtained by certain of our patients. These experiences are the basis of the six major criteria which at present are the guide in selection of cases deemed suitable for this operation. These are as follows:

1. The "arthritis" should be chiefly periarticular or synovial (capsular) with little, if any, bony alterations (destruction or hypertrophy) except atrophy.

If marked bony alterations have occurred, resection of sympathetic ganglia and trunks is not expected to accomplish any definite restoration of the lost bone and cartilage. Furthermore, when the bony changes are marked, similarly extensive changes may have occurred in the soft tissue, with injury to the vascular supply, probably irreparable to a large degree.

2. Patients preferably should demonstrate some of the alterations in vasomotor tonus, shown objectively by cold, clammy, sweating hands and feet, reduction of blood pressure (approximately below 110 to 115 systolic), and subjectively by intermittent numbness and tingling.

When the extremities are already warm, the caliber of the vessels is presumed to be sufficient or nearly so, and resection of sympathetic ganglia and trunks would not be expected to increase materially the articular circulation. When arteriosclerosis is present adequate vasodilatation may be impossible of attainment even with operation. In the presence of either of these conditions the vasomotor index (Brown) will be low.

3. Vasomotor alterations must be capable of correction, or of overcorrection, by means of release from control of the sympathetic apparatus. The possibility of such correction can be demonstrated by determining the "vasomotor index";

TABLE I

TENTATIVE CLINICAL CLASSIFICATION OF DISTURBANCES OF THE JOINT BASED ON PRESUMPTIVE ETIOLOGY

1. Infectious arthritis
   - Known to be specific infectious, for example:
     - Tubercuious
     - Gonorrheal
     - Pneumococcic
     - Typhoid
     - Syphilitic (spirochetal, not arthropathy)
     - Staphylococcal (septic)
   - Probably specific infectious (with toxins)
     - Rheumatic fever (streptococci or their toxins)
     - Arthritis with amebic colitis (amebic or secondary streptococci or their toxins): rare
     - With ulcerative colitis (secondary streptococci or their toxins): rare
     - With certain skin diseases (especially psoriasis)
   - Nonspecific (chronic infectious type); streptococcal
     - Articular nonspecific infectious arthritis
     - Nonarticular localization (myositis fibrositis, lumbago)
2. Traumatic arthritis
   - Extrinsic trauma (generally acute): (1) articular (traumatic, baseball fingers), and (2) nonarticular (nun's knees and housemaid's knees, sprains, strains)
   - Intrinsic trauma (generally chronic): postural arthritis, static arthritis of obesity
3. Senescent arthritis, chief sites:
   - Fingers (Heberden's nodes)
   - Hips (morbus coxae senilis)
   - Hypertrophic spine of the elderly; cervical frequently, lumbar most common
   - Knees (often in combination with static arthritis of obesity)
4. Gouty arthritis
   - Acute (recurring with complete remissions)
   - Chronic (progressive with residual deformity)
5. Arthropathy
   - Secondary to lesions of the central nervous system (syringomyelia, Charcot's disease)
   - Secondary to certain lung conditions (pulmonary osteoarthropathy)

that is, by obtaining definitely higher cutaneous temperature than mouth temperature after typhoid vaccine has been given intravenously. The temperature of the joints of the extremities may or may not be identical with that of the skin over them, but the temperature of the latter serves as an available index of elevation of temperature from vasomotor dilatation.

The "vasomotor index" is determined as follows: fifty million "triple typhoid" bacilli (typhoid, paratyphoid A and B) are given intravenously. The

oral temperature may rise but 2° C., whereas the cutaneous temperature over the joints of the extremities may increase 10 to 14° C., a ratio of 1 to 5 or 1 to 7. The best results seem to occur in cases in which the ratio is high and in which the increase in temperature is more than 5° C.

4. The patient should be preferably less than thirty-five years of age, and not more than the age of forty-five years.

Chronic "infectious" arthritis generally appears before the age of thirty-five or forty years. The majority of cases of arthritis in patients who are more than the age of forty-five years belong to the type here called chronic senescent (degenerative, hypertrophic) arthritis. Furthermore, after the age of forty-five years, the presence of arteriosclerosis, preventing adequate vasodilatation, may act as a contraindication.

5. The arthritis should be progressive, and the main disability should be confined to the extremities, particularly to the hands and feet. If the arthritis is not progressive, continuation of the therapeutic program already established may accomplish satisfactory results. If it does not, and if the degree of disability is great, operation may be permissible in carefully chosen cases.

TABLE II

CLASSIFICATION OF CHRONIC ARTHRITIS IN MOST COMMON USE

AUTHOR	FIRST TERMINOLOGY*	SECOND TERMINOLOGY*	TERMINOLOGY BASED ON
Goldthwaite	Atrophic	Hypertrophic	Pathologic changes (bone)
Nicholls and Richardson	Proliferative	Degenerative	Pathologic changes (soft tissue and bone)
English	Rheumatoid	Osteoarthritis	Clinical data
Fisher	Synovial	Chondro-osseous	Anatomic site
Various authors	Periarticular	Hypertrophic Destructive	Roentgenogram

*The terms in this column are in general synonymous.

6. A reasonable period, probably at least six to twelve months, of intensive, not haphazard treatment by the more established, less radical procedures, should be allowed before resection of sympathetic ganglia and trunks should be considered. However, rapidity of progression or stress of economic circumstances may necessitate consideration of earlier surgical measures.

There will be wide variation in what is considered to constitute a reasonable period of treatment, and more particularly as to what is meant by adequate previous treatment. No one patient probably ever had all the various forms of treatment deemed by various observers to be adequate. For the individual clinician, decision on this point will rest on the failure, first of that program, whatever it is, which has in general been for him the most successful, and with the additional failure of such other promising, but by him less consistently used, measures that he feels are worthy of trial.

Operation of Limited Application.—On a few occasions we have been led, by stress of a patient's progressive physical and economic disability and his desire for operation, to perform resection of sympathetic ganglia and trunks in the presence of definite, bony and cartilaginous alteration. In general the results have been disappointing as to the degree of reduction of symptoms, inflammation and articular stiffness obtained. Of course bony alterations already

present were unaffected. In some, pain was not greatly alleviated nor progression of the condition markedly influenced. In some, the marked improvement noted in the early postoperative course was not maintained. This was not the universal outcome, however. In at least the following case relief of pain was obtained in joints in which the arthritic process had gone on to include definite hypertrophic and destructive changes, with considerable deformity.

REPORT OF CASE

A woman, aged twenty-six years, began to have arthritis in the hands especially, but also in the feet. Twelve years before she came to the clinic she had had two periods of relative quiescence, respectively of two and two and a half years' duration. The last exacerbation had started in February, 1929, after which time the arthritis had been markedly progressive. The arms, elbows, and hands, especially, were very painful. The arthritis progressed steadily in spite of treatment which included extraction of several teeth, appendectomy, many prolonged periods of intensive physiotherapy, several courses of administration of typhoid vaccine intravenously, a diet high in calories and vitamins and directed against constipation, several weeks' treatment by colonic irrigation, and a diet high in Vitamin B, and two series of treatments by roentgen rays. The tonsils had been removed prior to the onset of the arthritis. There was marked ulnar deflection of both hands, and contraction deformities of the fingers. The hands especially were cold, clammy, and painful, and there was flexion deformity of the elbows, without complete ankylosis. The shoulders were mobile but painful. The knees and feet were involved to a less degree than the hands.

Roentgenograms gave evidence of marked destructive and hypertrophic changes, particularly in the fingers, wrists, elbows, and feet, with periarticular changes in the shoulders and knees. The vascular index for the right index finger was 4.

Because of the progressive pain, resection of sympathetic ganglia and trunks was suggested, in spite of the definite bony alterations. It was done, in the cervical region, with the hope of relieving pain and possibly checking the progress of the disease, particularly in the joints, in which thus far changes were in soft tissue only.

Although the deformity and bony changes present at the time of operation are in the main unaltered, at least to date (six months postoperatively), the patient has experienced marked analgesic effects from the cervical operation (Table III) and in addition has less stiffness and more muscular strength in the hands. Because of this, she requested that the lumbar ganglia and trunks be resected also, and this has just been done.

TABLE III

DECREASE OF PAIN IN JOINTS FOLLOWING CERVICOTHORACIC SYMPATHETIC GANGLIONECTOMY PERFORMED TO RELIEVE PAIN (IN SPITE OF THE PRESENCE OF SOME BONY CHANGES)*

JOINTS	BEFORE OPERATION, GRADE		FORTY DAYS AFTER OPERATION, GRADE			FIVE MONTHS AFTER OPERATION, GRADE		
	AT REST	ON VOLUNTARY MOTION	AT REST	ON VOLUNTARY MOTION	ON FORCED MOTION	AT REST	ON VOLUNTARY MOTION	ON FORCED MOTION
Right hand	2	3	1	1	2	0	0	1
Left hand	1	2	0	0	1	0	0	1
Right elbow	3	3	0	1	1	0	0	1
Left elbow	2	2	0	0	1-2	0	0	1
Right shoulder	1	1	0	0	1	0	0	0
Left shoulder	1	1	0	0	1	0	0	0
Right wrist	2	3	0	1	2	0	0	1
Left wrist	2	2	0	1	2	0	0	1

*Pain graded on the basis of 0 to 4.

Operation not Indicated.—There are certain types of chronic infectious arthritis in which resection of sympathetic ganglia and trunks is not advocated.

Some of these types have been mentioned; namely, cases of chronic infectious arthritis with definite bony involvement, cases in which the extremities are already warm and the caliber of the arteries is maximal or nearly maximal, and cases in which arteriosclerosis probably would prevent vasodilatation. Another type is chronic infectious arthritis involving the spinal column. Surgical technic by which resection of sympathetic ganglia and trunks can be applied in arthritis of this structure is not available. Still another type for which the operation is not advised is chronic infectious arthritis involving the hips and shoulders. When the process is localized in the elbows or knees resection of sympathetic ganglia and trunks may afford more chance of relief than it does for involvement of the shoulders and hips. However, limited relief has been obtained in disease of these regions, as compared with that of the hands and feet, possibly because the temperature of these joints is so much less elevated by the operation. Furthermore, the operation is not advocated for chronic arthritis of the types generally considered noninfectious: the forms designated as degenerative arthritis, osteoarthritis, and hypertrophic arthritis. These forms are generally more localized and less polyarticular in nature.

TECHNIC

Since the technic of resection of lumbar sympathetic ganglia and trunks has been previously described by Brown and Adson and remains unchanged, it will not be outlined here. The technic of the cervicothoracic operation has been modified somewhat from that of previous descriptions. It was noted that by the technic formerly used, the manifestations of Horner's syndrome were not always equal on both sides. This suggested that gray, postganglionic fibers were entering the carotid plexus; therefore Adson has changed the operative procedure by resecting the vertebral portion of the first rib instead of the second. The lateral portion of the transverse process is also resected with the rib in order to facilitate the exposure. This permits entrance into the mediastinum opposite the first thoracic sympathetic ganglion. The first thoracic ganglion is then dissected free and the trunk is resected just above or below the second thoracic ganglion, depending on whether the second is situated high or low with relation to the second thoracic nerve. If the second thoracic ganglion is not removed, the first thoracic nerve is carefully dissected from the intervertebral foramen to its juncture with the brachial plexus in order to interrupt thoroughly all gray rami that may ascend from the second thoracic ganglion. After elevating the thoracic ganglia and trunk, the entire lower cervical ganglion is resected with the chain. This alteration in the technic has produced complete and permanent bilateral Horner's syndrome, and, it is hoped, has included all vasoconstrictor fibers to the upper extremities.

EFFECTS

Physiologic.—The recognized physiologic effects of the operation are apparently without deleterious results, if one views as justifiable by-products, the Horner's syndrome, dryness of the skin and absence of sweating. This statement is made after an experience at the clinic of five years since beginning such operations, first on patients with spastic paraplegia. Then it was applied suc-

cessively in cases of Raynaud's disease, thrombo-angiitis obliterans, scleroderma and arthritis. The physiologic effects may be summarized as follows:

1. Marked vasodilatation. This was illustrated in injections performed by Horton and Craig. The vasodilatation apparently affects chiefly the moderate and small arteries and arterioles. There is probably no vasodilatation of the capillaries. At least the capillaries of the nailfold are constricted after the operation, but the rate of flow is augmented.

TABLE IV

STUDIES OF SURFACE TEMPERATURE IN CHRONIC "INFECTIOUS" ARTHRITIS BEFORE AND AFTER LUMBAR SYMPATHETIC GANGLIONECTOMY

CASE	FEET*				
	BEFORE OPERATION, DEGREES C.		ABOUT 2 TO 3 WEEKS AFTER OPERATION, DEGREES C.		AVERAGE INCREASE, DEGREES C.
	RIGHT	LEFT	RIGHT	LEFT	
2	23.8	23.2	28.4	28.6	5.0
4	25.3	26.2	30.2	31.0	4.8
5	25.7	27.2	33.5	34.0	7.3
6	23.8	25.0	34.6	35.0	10.4
7	27.8	28.4	33.8	34.6	6.1
8	28.5	27.6	32.2	32.0	4.0
9	25.4	25.0	33.4	32.9	7.9
10	28.1	25.6	33.9	33.1	6.6
11	24.1	24.7	33.1	32.8	8.5
12	22.4	23.0	34.5	34.0	11.5
14	20.2	20.3	33.8	34.0	13.7
15	26.2	25.9	33.6	33.9	7.7
16	25.5	26.8	33.0	32.9	7.3
17	26.2	25.7	34.0	34.7	8.4

*Average increase in temperature, 7.8°C.

TABLE V

STUDIES OF SURFACE TEMPERATURE IN CHRONIC "INFECTIOUS" ARTHRITIS BEFORE AND AFTER CERVICAL THORACIC SYMPATHETIC GANGLIONECTOMY

CASE	HANDS*				
	BEFORE OPERATION, DEGREES C.		ABOUT 2 TO 3 WEEKS AFTER OPERATION, DEGREES C.		AVERAGE INCREASE, DEGREES C.
	RIGHT	LEFT	RIGHT	LEFT	
3	29.0	29.3	34.5	34.7	5.4
13	28.4	28.2	33.8	34.1	5.6

*Average increase in temperature, 5.5°C.

TABLE VI

STUDIES OF SURFACE TEMPERATURE IN CHRONIC "INFECTIOUS" ARTHRITIS BEFORE AND AFTER LUMBAR AND THORACIC SYMPATHETIC GANGLIONECTOMY

CASE	BEFORE OPERATION, DEGREES C.				AFTER OPERATION, DEGREES C.				AVERAGE INCREASE, DEGREES C.	
	FEET		HANDS		FEET		HANDS			
	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	FEET	HANDS
1	25.9	24.1	23.5	24.1	34.5	34.0	33.9	33.3	9.3	9.8

2. Definite increase of temperature of the extremities, as determined by studies of surface temperature with the Stewart-Kegerreis calorimeter and Sheard electrothermocouple. In the hands and feet, the temperature may in-

crease 5 to 13° C., in the elbows and knees generally not more than 2 to 4°, and in the shoulders and thighs, approximately only 1 to 2 or 3° (Tables IV, V and VI).

3. Abolition of reflex sweating. If areas of sweating persist in the upper extremities after the operation they have been considered evidence of incomplete ramisection. An operation anatomically correct in technic is followed by complete abolition of reflex sweating.

4. Loss of pilomotor reflex.

5. The reaction of cardiac acceleration not markedly disturbed. There is apparently no marked alteration of cardiac rhythm or rate.

6. A Horner's syndrome which is permanent if the operation is anatomically correct. It does not give rise to significant alteration of vision, however.

7. Some minor atrophy of shoulder muscles in the region of the wound after cervicothoracic operation.

8. No objective atrophy of muscles of the lower extremities after the lumbar operation. Instead they may enlarge and again become fusiform.

9. Relief of pain of variable degree. In the extremities the degree and rapidity of analgesia may be gratifying. Relief of pain precedes the other beneficial effects that may result, such as diminution of redness, tenderness, swelling, and stiffness. On awakening from the anesthetic several patients experienced unusual, even complete, relief of pain. Increased warmth of the extremities occurs as the immediate result of the operation. In some cases the relief of pain was maintained; in others it was not. In some cases relief of pain has been only partial at first, and has become complete within eight weeks to six months after operation. In other cases, relief has never been complete and in some cases there has been no diminution of pain. With further experience in selecting and managing cases it is hoped that relief of pain can be expected to be maintained.

A satisfactory explanation of analgesia by resection of sympathetic ganglia and trunks cannot be given. Craig has commented on it briefly thus:

"There are two chief theories concerning this subject: (1) that the sympathetic nerves carry sensory fibers, and (2) that the sympathetic nervous system regulates in some manner the threshold of pain. The last theory seems to be the most logical. Here at the clinic we have not been so fortunate as to obtain 100 per cent good results in our operations on the sympathetic nervous system (for other conditions as well as for arthritis) for indefinite pain. If operation on the sympathetic nervous system is attempted in every case of indefinite pain, then the procedure will fall into disrepute."

Clinical.—To date bilateral resection of cervicothoracic sympathetic ganglia and trunks only, has been performed at the clinic in two cases, bilateral resection of lumbar sympathetic ganglia and trunks only, in twenty-five cases, and both procedures in three cases. The results in those cases in which operation has been performed most recently will not be considered here. The preliminary results in the first seventeen cases have been reported elsewhere and need not be reviewed here. The patients, however, can be considered to have fallen into three groups:

1. Those who have obtained partial to almost complete relief from the manifestations of their arthritis, and in whom the relief to date has been maintained or progressive.

2. Those who have obtained rather marked relief for a few weeks after operation but in whom there have been partial or complete relapses.

3. Those who have obtained negligible relief.

To aid in justifying a major operative procedure such as resection of sympathetic ganglia and trunks one would hope that at least primary beneficial results would be evident within three weeks to three months after operation or that the improvement would be maintained and progressive.

In some cases there has been reduction of pain, indeed complete absence of pain, immediately after operation, with a slower reduction of redness, swelling and stiffness and perhaps no reduction of deformity. Because the analgesia is maintained, however, it seems justifiable to consider such results as definitely successful.

When there is improvement after operation, for weeks or months, if the process then returns in the joints the vasomotor control of which has been released, the procedure cannot be considered successful. Reinfection from other affected joints may be the cause of these exacerbations, but if the operative procedure cannot prevent this, it cannot be considered a success.

Certain other operative procedures for arthritis advocated by others from time to time (for example resection of the colon) have resulted in temporary success. It has been argued that the results came from the postoperative period of rest and the sharp metabolic stimulation of an operation, and that the specific operation itself was of no value. In attempting to evaluate resection of sympathetic ganglia and trunks dispassionately, we must remember that the factors of three or four weeks of rest after operation and the stimulation of the defensive forces of the body by the operation are possible factors in producing relief. Further experience and longer postoperative observation must be had before the degree and field of usefulness of the operation can be determined.

Flothow and Spurling have both reported satisfactory results in five cases of chronic polyarthritis.

SUPPLEMENTARY TREATMENT

In certain cases in which rather definite relief of pain resulted from the operation, patients were inclined to overexercise the joints. This may prevent reduction of swelling, stiffness, and redness. Patients must be prevented from causing too great trauma to the joints. Exercise should be extended with more careful attention to the reaction, not of pain, but of other signs of inflammation.

When a reasonable period of time has passed for judging the results of the operation itself, other rational procedures in treatment should be resumed. Complete removal of foci of infection presumably will have been done before operation was considered. Continuation of careful massage, muscular training, exercises, reduction of deformity, and protection of weakened joints by mechanical means are all indicated. Application of heat to the extremities is also rational, for although maximal dilatation presumably is accomplished in the

most distal joints of the extremities, it will be remembered that the increase in temperature in the less distal joints of the extremities is not nearly so great.

CONCLUSIONS

Resection of sympathetic ganglia and trunks is not applicable to all forms of arthritis, nor is it useful in all stages and degrees of chronic infectious arthritis. In this experimental stage it is our impression that it is of definite value in certain carefully selected cases. It seems to be a justifiable procedure in these selected cases when all other reasonable measures have failed. Used properly, but not delayed too long, it may, by maintaining increase in temperature, circulation, and perhaps metabolism of the more distal joints of the extremities, induce a stage of compensation in the arthritic disability that is not capable of production otherwise. Our final opinion regarding the proper selection of cases for the operation, and its value in these cases, cannot yet be expressed.

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PAIN OF NERVE ROOT ORIGIN IN HYPERTROPHIC OSTEARTHRITIS OF THE SPINE AS A CONFUSING FACTOR IN DIAGNOSIS

By Lewis Gunther, M.D., Los Angeles, Calif.

OSTEARTHRITIS of the spine may be the cause of pain and sensory disturbances of spinal root distribution, either from the meningeal reaction secondary to the ostearthritic process or from pressure in narrowed canals. The radicular syndrome in hypertrophic ostearthritis of the spine, described elsewhere, was based on the study of 70 patients at the University of California Medical School.*[1] Adequate descriptions of a root type of disturbance occurring in diseases of the spinal vertebrae and nerves other than in hypertrophic ostearthritis may be found in systems of medicine[2] or in standard textbooks.[3] These will not concern us at this time.

When one considers the anatomic distribution of the spinal nerve roots, and the fact that the skin of the entire body, except part of the face and the anterior third of the head, contains sensory receptors for the spinal roots, it becomes obvious at once that, depending on the level of the pathologic process in the vertebrae, symptoms at the periphery will be manifested as painful or unpleasant sensations in areas that are also common sites for the reference of pain from various diseased viscera. (Figs. 1 to 10.) It is not surprising, therefore, that a case history analysis revealed the variety of diagnoses shown in Table I.

Clinical History.—Sufferers from hypertrophic ostearthritis of the spine described the root areas of their chief symptoms with topographic accuracy. The extent of the painful area was accurately demarcated regardless of the region involved and was usually bilateral. In the past history, one could obtain the story of involvement of areas not complained of at the time. These, too, the patient demarcated with precision. The history of long standing revealed a story of involvement of various areas over a number of years and if a record listing the subjective areas according to the roots involved was made, one could anticipate the vertebrae that would show the pathologic process on the x-ray examination. Certainly the sharp demarcation and accurate localization of the painful areas, with involvement of the entire cutaneous distribution of the particular roots was a constant finding and in contrast to the usual vague localization and incomplete root zone distribution of the pain of the classical viscerosensory reflex.

Clinical Course: Mode of Onset: Duration and Description of Pain.—Although the root pain of ostearthritis might appear abruptly, the onset of the pain was not sudden in the sense of it constituting a seizure as one encounters in abdominal colics or in angina pectoris. The pain lasted for a variable length

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of time from a few minutes to hours, and might disappear as quickly as it appeared. More often the cessation of pain was gradual or tapered off if a comfortable position was found.

The pain was generally bothersome and nagging and was usually described as an aching, soreness or as a paresthesia. Certain movements of the spinal column which the patient described by such phrases as: rising after a sitting position, raising the head on awakening, getting out of bed, walking, lifting, sitting in one place for any length of time, a change of position, and the acts

TABLE I

VERTEBRAE AFFECTED	THE CHIEF COMPLAINT OR DIAGNOSIS	THE NUMBER OF DIAGNOSES OCCURRING IN 70 PATIENTS
C2-3	Headache	8
	Thyroid disease	1
C4 or 5	Painful shoulders	
	Painful arms	
C4 or 5 with C6 and 7	Sore neck	
	Neuritis	
	Neuralgia	
	Arthritis of shoulder	
	Stiff neck	18
	Fibrositis or myositis	3
D1 to 5	Heart disease	
	Angina pectoris	
	Heart neurosis	50
	Pulmonary and pleural disease	2
	Painful breast tumor (size of pea)	1
D6 to 9	Stomach trouble	14
	Peptic ulcer	6
	Patients who first visited a gastroenterologist for ulcer	3
	Gall bladder disease	4
D10 to 12	Lower abdominal pain	15
	Chronic appendicitis	4
	Pelvic disease	4
	Varices of broad ligament (laparotomy was not performed)	1
L1 to 4	Meralgia paresthetica	6
L4-5, and Sacral	Sciatica	23

The multiplicity of diagnoses is accounted for by the fact that the same patient was seen in various special clinics because of a preponderance of symptoms varying from one area to another at different visits. Such shifting of the chief complaint in the same patient from time to time is in itself suggestive of root pain in an individual who is suffering from diffuse involvement of the spine in the osteoarthritic process.

of coughing, sneezing and straining, caused the pain to appear or to become aggravated. The acts of coughing, sneezing, and straining in the production or aggravation of symptoms was very helpful in the diagnosis of the condition. Pain at night which awakened the patient or prevented sleep and was relieved by a change of position such as by "turning over" was commonly noted. In the far advanced, widely distributed vertebral process, the inability to sit up in bed from a supine position without producing pain and the necessity of rolling out of bed on one side or the other were quite characteristic.

Even though the pain in our cases was never severe enough to require opiates, sometimes, in the aggravated forms, it prevented or interfered with work more by virtue of its constant exacerbations following movements of the spine than from its severity. In the extreme forms and to a variable degree in the lesser forms, the sufferer had pain over the various root zones from morning to night, at rest, or in sleep. The pain appeared in one region or another when the head was raised from the pillow in the morning and disappeared after the patient had been up and about for a while, only to return when active movements were again begun. Only temporary relief was obtained by resting in a chair, for on prolonged sitting the pain returned. Later sleep was broken by the appearance of symptoms which necessitated a change of position for relief.

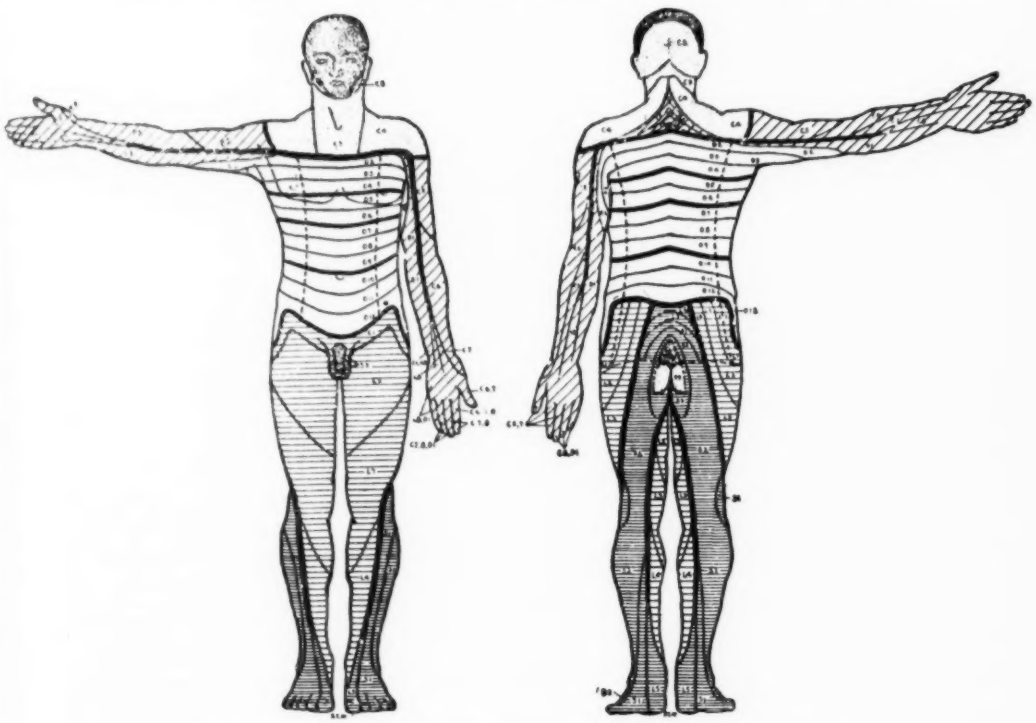

Fig. 1.—Radicular sensory innervation (Mayer, J. A. M. A., 1918).

But ordinarily, during the daytime the patient was aware only of a disagreeable sensation. He was uncomfortable and nothing more. While seated, during the taking of the history he would tell the examiner that he had pain and would then proceed to outline it and to describe its character. Other than the patient assuming some particular posture for comfort, such as leaning toward one side or the other, there were no outward signs to disclose the presence of his pain.

Often, as when the precordium was the seat of the chief complaint, worry and fear over the constant discomfort might be the chief reasons for the visit to the physician. In such instances when the patient was asked whether he would have consulted a physician if the disorder was strictly confined to the right side, he might reply: "No, I would pay no attention to it then, because

Fig. 2.—Radicular distribution, cervical 1, 2 and 3; occipital and vertex "headache."

Fig. 3.—Radicular distribution, cervical 1, 2 and 3; cervical 5 to 7; occipital and vertex "headache"; and back of the neck, pain.

Fig. 4.—Radicular distribution, cervical 4, painful shoulders; cervical 5 to 7, back of the neck, pain.

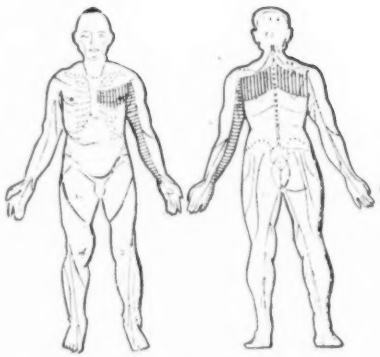

Fig. 5.—Radicular distribution, dorsal 2 to 5, "pseudo-angina pectoris."

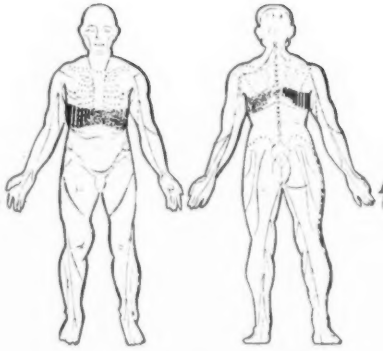

Fig. 6.—Radicular distribution, dorsal 6 to 9; area of referred gall-bladder pain on the right; gastric disturbances and pancreatitis.

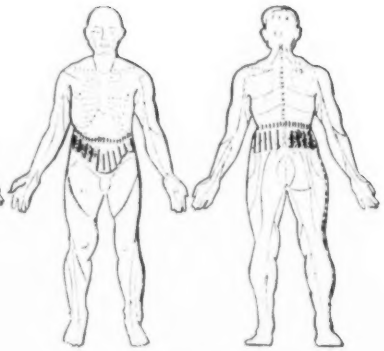

Fig. 7.—Radicular distribution, dorsal 10; belt-like pains as in tabes; dorsal 11, 12 on the right; area of referred pain from acute appendicitis, and on the left, area of referred pain from adnexal disease.

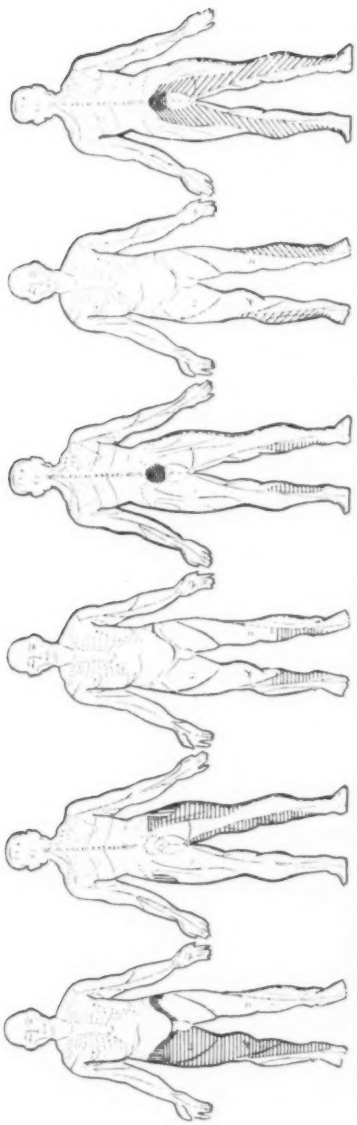

Fig. 8.—Radicular distribution, lumbar 1, 2, 3, 4; meralgia paresthetica, hip-joint and knee-joint disease.

Fig. 9.—Radicular distribution, lumbar 4, 5 and sacral 1, over the sacrum, lumbar 4, inner side of legs.

Fig. 10.—Radicular distribution, lumbar 4, 5 and sacral 1, over the sacrum with radiation over sacral 1 and 2, commonly spoken of as "sciatica."

the heart is not on that side." During the manipulations of the spine, in the course of the physical examination, certain movements of the spine would reproduce symptoms. Unless the patient called attention to the pain elicited during the manipulation, the examiner would not ordinarily be aware of its presence because of the lack of outward signs to disclose the condition.

From time to time the site of the predominating symptoms shifted. At one examination the precordium occupied the patient's attention, and at another the small of the back and the front of the abdomen, or the area over the gall bladder and the back across the shoulder blades. Again it was chiefly occipital and vertex headache or shoulder neuritis and pain between the shoulder blades. The occurrence of pain, often many times in the twenty-four hours, depended on the nature of the patient's activities. The duration of the pain did not seem to bear any relation to the frequency of the onset or the disappearance of symptoms. The painful areas were similar in their symptomatology and their response to remedial measures and they varied only in their regional location and intensity. The wearing of a corset or light brace, strapping the back, and heat and massage were measures that gave relief. Many of the patients preferred a hard bed, obtaining most rest when lying flat on the back, and the placing of boards under the mattress sometimes solved the problem of broken sleep at night. Because of the variable zonal symptomatology, the patient was apt to be ailing over long periods of time and to become a chronic complainer. In the clinic, his chances of becoming labeled a neurotic were very great.

The Physical Examination.—The physical examination revealed evidences of hypertrophic ostearthritic processes in the peripheral joints as well as in the spine, although the former were not invariably present. The usual findings consisted of Heberden's nodes on the fingers, or grating or crackling in the knee joints, shoulder joints or in the neck, with variable degrees of restriction in the mobility of the affected joints. The spine generally showed restricted mobility of various degrees. The normal dorsal anterior bowing may have become exaggerated or flattened out in its upper or lower part. Sensory alterations to light touch as tested with the cotton tuft on a wooden applicator, and sensory disturbances such as hyperalgesia or hypalgesia to pinching could be demonstrated. The roentgen-ray findings have been described in detail elsewhere.[1]

Treatment.—Temporary relief of pain was offered by the use of the coal tar derivatives and other analgesics. Salicylic acid, phenobarbital, and codeine were helpful. Main reliance was placed on physical therapeutic measures, such as baking, heat, and massage, and the immobilization of the spine in a properly fitted corset or a Taylor brace. Heat alone was found to be the most satisfactory agent for the milder cases. Vasodilators such as nitrites were without effect on the pain. Recently Swain[4] has reviewed the subject of treatment and has suggested means of preventing the deformities associated with hypertrophic ostearthritis of the spine.

Conclusion.—Ostearthritis of the spine is a common cause of pain of spinal root distribution. The syndrome of root pain in ostearthritis of the spine and its means of clinical description has been described.

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CHRONIC ARTHRITIS: ITS CLASSIFICATION, ETIOLOGY AND PATHOLOGY WITH AN OUTLINE OF ITS RATIONAL TREATMENT*

By Leonard W. Ely, M.D., San Francisco

A JOINT usually consists of a closed cavity, bounded by the articular cartilage, usually hyaline, and by a connective tissue membrane, the synovial membrane. These two structures meet at the articular margin of the end of the bone, and the structure of one seems to merge into that of the other, so that no exact termination can be made out between the two. In other words, the synovial membrane is not continued over the surface of the articular cartilage. The perichondrium is nonexistent in the normal joint after fetal life.

The articular cartilage consists of encapsulated cells, and of a hyaline basement substance. It contains no blood vessels, and is therefore not subject to inflammation. There is therefore no such thing as a chondritis. Strictly speaking the same may be said of an osteitis. The bone simply reacts to changes of its contained marrow; hence the absurdity of such terms as osteochondritis. The synovial membrane is the only tissue of a joint which can be subject to an inflammation. It is the active tissue of the joint. A synovitis therefore is an arthritis, and an arthritis is a synovitis. The marrow in the vicinity may or may not be inflamed.

Arthritis is usually divided into acute and chronic. The division is a convenient one but by no means exact. The line between the two is often not clear; a case which begins with all the characteristics of an acute arthritis may subside into a chronic state, and an essentially chronic arthritis may at any time exhibit acute manifestations.

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Chronic arthritis has been variously classified. The confusion in the classifications is so great that a student is often puzzled to understand an author's meaning. Again some of the classifications are so involved that it is almost impossible to remember them. Arthritis deformans means one thing in Germany, another in England, and several things in America. In point of fact it means a deforming inflammation of a joint, and any arthritis may be that. Osteoarthritis to one, is hypertrophic arthritis to another; degenerative arthritis to a third; and arthritis deformans to a fourth.

In all the history of medicine two methods of advance have been followed, but rarely side by side. One usually crowds out the other. They may be called the deductive and inductive, the philosophic and the experimental, or the speculative and the investigative. The one, on the basis of a few observations, attempts to arrive at a conclusion by a process of abstract reasoning, and backs up the conclusion by extravagant claims of cures; the other accumulates a mass of facts, and reaches its conclusions with relatively little reasoning. The first is easy, rapid, frequently profitable, and almost invariably sterile. It is the method of the past, and has been generally discarded except in diseases of the joints. Here it is too often followed. A knowledge of the pathologic anatomy of the joints, and of the reaction of their tissues to injury and disease is usually considered superfluous. It is no more superfluous here than in any other branch of medicine. No one who does not possess it deserves an audience.

We have learned much on the subject of chronic arthritis during the past fifty years—little before that, and nothing except from a patient accumulation of facts. Our experience should teach us that here, as elsewhere in medicine, we can expect little from ratiocination. What follows is based upon (1) clinical experience; (2) laboratory study of the pathology of arthritis; (3) experimental work on animals to test the truth or falsity of a theory.

CLASSIFICATION OF CHRONIC ARTHRITIS

The customary procedure is first to describe cases of known etiology under their own headings, tuberculous, syphilitic, etc., and then to classify the cases of unknown etiology according to some feature, clinical or pathologic, which the observer deems important. This is unscientific, confusing, and subject to frequent change. All cases of chronic arthritis fall into two classes or groups, which are as different as black is from white, and which can almost always be distinguished by clinical investigation, aided by the x-rays. They can always be identified when the material is examined in the laboratory. They have been called by many names.* Nichols and Richardson's nomenclature probably comes nearest the truth.[1] Until many obscure points have been cleared up I prefer to call them Type 1 and Type 2.

THE TWO GREAT TYPES OF CHRONIC ARTHRITIS

First Type.—This includes all the infectious arthritides, e.g., tuberculous, syphilitic, and also those cases whose exact etiology is not yet known, and

*A tuberculous joint in the old days was a fungous or strumous joint, or a caries sicca.

which are called by various names, e.g., rheumatoid, proliferative, atrophic. Reading teaches us that these latter form a slowly dwindling group. Tuberculosis, syphilis and others formerly belonged to it, perhaps under the caption of chronic "rheumatism."*

Second Type.—The cause of this type has never been determined. The disease forms a clear-cut entity, and has been identified under various names, senile rheumatism, arthritis deformans (German), osteoarthritis (English), hypertrophic arthritis (Goldthwait), degenerative arthritis (Nichols and Richardson), etc. When it occurs in the fingers it is known as Heberden's nodes, and is often mistaken for gout. In the hip it is sometimes called morbus coxae senilis.

THE FIRST GREAT TYPE OF CHRONIC ARTHRITIS

The members of this group enjoy a common pathology. It follows therefore that their symptomatology and their radiologic characteristics are the same. So much alike are they indeed, that, if the patient were covered with a sheet, exposing one joint for examination, we should be completely at sea. The diagnosis is usually made from the history, and from a general examination of the patient. A positive diagnosis can be made only by a demonstration of the causal organism. In some of them, as in the arthritis caused by the tubercle bacillus, the oidium coccidioides, or the pus cocci, this is simple, and is a routine procedure. In others, such as syphilis, it is much more difficult, and is rarely done. If an arthritis is clinically syphilitic, we almost invariably rely upon the therapeutic test. In a gonococcic arthritis the organism may be recovered from the joint on one day, and not on the next. In a patient with an acute gonorrhea, whose knee suddenly swells and becomes exquisitely painful, we usually make the diagnosis with or without the recovery of the gonococcus. There must be an ability in the synovial membrane to conquer infections, for gonococci in the synovial membrane have not the same significance as they have in the heart valves. Indeed, there is such a power in the synovial membrane, for gonococcic joints often recover completely with or without rational treatment.

This group includes also many cases whose exact etiology is still in doubt. Until the causal organism or organisms shall have been recovered from them with reasonable frequency scientific scepticism is justified. The reasons why I believe that they are all infectious are:

1. They enjoy a pathology and a symptomatology similar to that of the known infectious arthritides. If a piece of the synovial membrane be submitted to a microscopic examination, the pathologist reports chronic inflammation, tuberculous or nontuberculous as the case may be.

2. Various investigators, notably Poynton and Paine, by diligent search have recovered infectious organisms from some of these obscure cases. Others have sought for them in vain. In this connection it must be remembered that in some infectious arthritides bacteria are fed into the synovial membrane intermittently from a distant focus, as are the gonococci in a urethral infection.

*I have heard heated discussions as to whether there was any such thing as syphilitic arthritis. In Albutt's *System of Medicine*, published about twenty-five years ago, the statement is made that gonorrheal arthritis is caused by a reflex irritation of the urethral mucous membrane.

If we do not find them we infer that they have been present, from the characteristic changes which they have left behind them in the joint tissues, as we recognize a safe breaker from his finger prints on the safe, or a woodchuck from his characteristic burrow.

With the second type of arthritis, bacteria have nothing to do, and can be present only as an accident. Indeed in this second type of arthritis the joint seems to be practically immune from bacterial invasion. I do not remember ever to have heard of a so-called second type joint being infected after an operation.

3. Every case of arthritis of this type whose cause is known, tuberculous, syphilitic, gonococcic, typhoid, pneumococcic, etc., is due to infection from a distant focus. Reasoning by analogy, we conclude that other cases of unknown cause, but of similar pathology, are due to the same thing.

4. Many cases of intractable arthritis recover promptly after the removal of infected tonsils or after the cure of an infection in the deep urethra. To base a method of cure on such an argument as this is unjustifiable, but to employ it as confirmation of other evidence is justifiable.

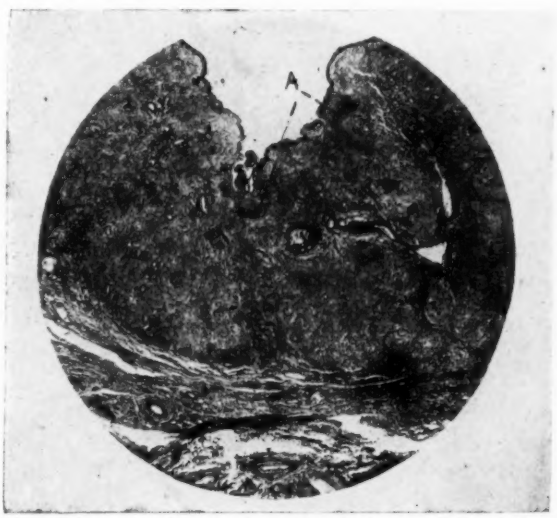

Fig. 1.—Tuberculosis of the synovial membrane, with thickening, infiltration, and villous proliferation. This is the rapid, severe form with practically no effort at encapsulation. Areas of necrosis at *A*.

PATHOLOGY OF TYPE I ARTHRITIS

The prime pathologic feature of this type of arthritis is, as Nichols and Richardson first pointed out, a proliferative inflammation in the synovial membrane (Fig. 1). To this may or may not be added a proliferative inflammation in the bone marrow in the immediate vicinity of the joint. This inflammation may start in either tissue and spread to the other. Certain easily understandable changes follow, not only in the marrow and in the synovial membrane, but also in the bone and in the cartilage. Let us first consider those cases in which the inflammation starts in the joint tissues themselves, that is, in the synovial membrane.

The synovial membrane becomes thickened, infiltrated, and villous. Sometimes the villous proliferation becomes extreme, and the villi form masses (Fig. 2). Usually an exudate is poured out into the joint cavity, serous, bloody, fibrinous, flocculent, or purulent, as the case may be. The fluid, to-

gether with the thickening of the capsule, causes the joint to swell. In some cases the original proliferation may be small in amount, and free fluid cannot

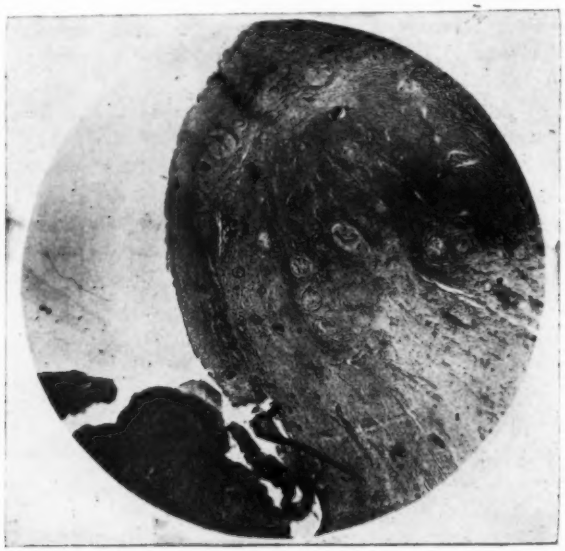

Fig. 2.—Tuberculosis of the synovial membrane. In this patient the resistance was more active. Encapsulation of the tubercles is evident, and no necrosis. Elaborate classifications have been built up on the difference in the proportions of invasion and repair.

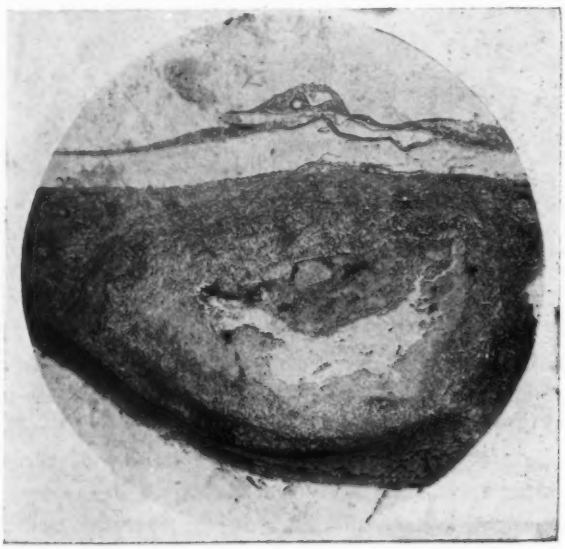

Fig. 3.—Old cheesy, encapsulated tuberculous focus, dug out of the fibrous adhesions in a resected ankle. The joint had been treated with apparatus years before, and had been considered cured.

be demonstrated. In them the formation of scar tissue may prevail. Adhesions form in the synovial membrane.

The cartilage becomes thinned, and the synovial membrane substitutes it at its circumference, and spreads out over its surface, giving the appearance

of a perichondrium. With the interference with the function, the cartilage itself becomes fibrous. In severe cases the cartilage may be bound tightly to the synovial membrane by adhesions, and to a lesser extent to the opposing cartilage. The joint cavity then is replaced by a mass of scar tissue, fibrous ankylosis. In some infections this fibrous ankylosis may become bony. In a supposedly cured tuberculous joint, collections of cheesy material may be locked up for years in the fibrous adhesions, ready at any time, when injury or unwise operative interference sets them free, to light up the disease afresh

Fig. 4.—Tuberculosis of the marrow immediately under the cartilage. Fingers of tuberculous granulations are beginning to push up through the cartilage. The cartilage is degenerating, and has become fibrous at its surface.

(Fig. 3). The muscles proximal and distal to the joint atrophy, and various circulatory changes may be added. On the other hand, as the result of appropriate treatment, or spontaneously, the disease may die out, and perfect function may return, even after what appears to be extensive change. This last occurs rarely if ever in a tuberculous joint.

When the disease starts in the marrow, it gains the under surface of the cartilage, the granulations absorbing or killing the bone trabeculae as they spread. They push up fingers through the cartilage (Fig. 4), and spread along its under surface (Fig. 5), interfering with its nutrition, and perhaps

killing it, gaining the joint either through it, or at its circumference. As soon as the synovial membrane is involved, it reacts as described above.

When much fluid accumulates in the joint cavity, it may rupture the capsule, and may then make its way to the surface; this, as is well known, is most likely in tuberculous and in suppurative infections.

SYMPTOMATOLOGY OF TYPE I ARTHRITIS

The symptoms are those of inflammation in any organ, pain, swelling, and interference with function. To these in the more active cases, redness, and increase of local temperature may be added. The pain is usually greater when the bone is involved than in the purely synovial cases. Sensitiveness to pressure is common. The swelling is in the soft parts. Bony proliferation

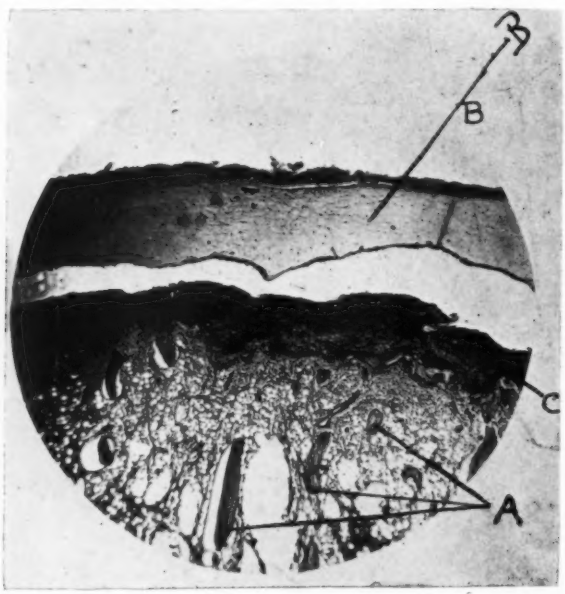

Fig. 5.—Tuberculosis of the marrow (*C*), directly under the cartilage (*B*). The cartilage has been sequestrated, and the bone trabeculae in the tuberculous area have practically disappeared. Bone trabeculae at *A*.

is absent in this type of arthritis. Flexion deformities are the rule, though superextension is often seen in the joints of the fingers. Limitation of motion is the rule, varying from a slight restriction at the extremes, to a complete ankylosis. Muscular spasm is common.

Constitutional symptoms may be present or absent, depending upon the nature of the infection, and upon its severity. Fever accompanies some, especially in their acute exacerbations. It is conspicuous by its absence in tuberculosis, when unmixed with a secondary infection. One does not expect any constitutional symptoms with a tuberculous joint, unless the patient has an active tuberculous lesion in some vital organ. Much the same may be said for syphilis, though here, as elsewhere in the body, this protean disease is wont to defy any rules laid down for it.

While no age is exempt, arthritides of this type are distinctly diseases of the earlier periods of life, in contradistinction to second type arthritis, which never occurs before the third decade, rarely then, and increases in frequency as age advances. The prevalence of lymphoid marrow in the bones of young persons explains the occurrence of certain of them, notably of tuberculosis and of syphilis. Necropsies in cases of typhoid have shown the constant presence of typhoid bacilli.[2] Acute suppurative hematogenous osteomyelitis is simply an inflammation of lymphoid tissue locked up in bone, and is therefore more frequent in young persons.

The x-ray characteristics of the type are swelling of the soft parts, thinning and irregularity of the joint space, and rarefaction of the bone. By the extent and distribution of this rarefaction the skilled radiographer is wont to make a shrewd guess as to the identify of the causal infection. In tuberculosis the rarefaction in the earlier stages may appear as a small area at the side of the film, just below the cartilage, or perhaps as a narrow streak beneath a portion of it. In the later stages the whole end of the bones may appear irregularly destroyed. This irregularity is a feature of tuberculosis. Bone production does not occur in the region of the joint in this type of arthritis. The light areas in the films of slow old cases of tuberculosis are due to deposits of calcium salts, not to bone. In all the slides of tuberculous bones I have examined I remember to have seen an indication of new bone formation in only one, and that was too small to have cast a shadow. The radiographer draws his conclusions from the shadow cast by the container of a sick tenant.

DIFFERENTIAL DIAGNOSIS

All these cases look alike. We strive first of all to place the case into the type to which it belongs, and then to find out its identity. This is never possible without the demonstration of the causal organism. We rely for a working hypothesis upon the history and upon a general examination of the patient. Each member of the class has peculiarities which enable us to recognize it in a large proportion of cases. When, after a long clinical experience, we think we can do more than this, we err. Ignorance of this fact is responsible for many extravagant claims of cure. Following are a few general rules:

Tuberculosis is uniarticular, and shows a preference for the larger joints. Muscular spasm and muscular atrophy are early and marked. The disease is irregularly progressive. The patient may be better this week than last, but next month he will be worse. Family history is important, not so much for the tuberculous diathesis on which we formerly laid such stress, as for the infection spread by a careless relative, or for the infection of several members of the family by the domicile or by the dairy herd. The tuberculous "habitus" is also unreliable. Many patients with tuberculous joints are otherwise strong and well. On the other hand, the presence of an active tuberculous lesion elsewhere in the body naturally influences us in our diagnosis.

Chronic Gonococcic Arthritis.—This is a misnomer. A gonococcic arthritis is probably always acute. The gonococcus does its work quickly, and dies out. What is known as chronic gonorrheal arthritis is caused by some other organism, probably by a streptococcus from a secondary infection in the deep urethra, following a gonorrhea. It is almost always multiple. The knees and feet are often involved, not only in their joints, but also in the bone directly under the tubercle of the calcaneus. In this case the pain may be great. The patient walks as if he were treading on eggs. Some cases of intractable old spinal arthritis are almost undoubtedly due to a lesion in the deep urethra.

Arthritis from *infection in the tonsils* frequently affects the joints of the hands and feet, and is also wont to be multiple. When the fingers are affected, the metacarpophalangeal and the proximal interphalangeal joints are the ones involved, in contradistinction to the arthritis of the second type, which affects the terminal interphalangeals. The knees suffer often.

Syphilis of the joints may imitate almost any form of arthritis of this type. It may be painful, contrary to the general idea, or painless, as in the knee synovitis of the late stages. It may involve the bone alone, or the synovial membrane. If the bone be involved, the synovial membrane usually escapes, in distinction to the other infections. In these, when the marrow in the bone end is diseased, the synovial membrane regularly participates. A positive Wassermann test is an indication, nothing more. A negative test means little. Hence the importance of the therapeutic test in the diagnosis.

The arthritis of *coccidioidal granuloma* imitates exactly that of tuberculosis. I know of no way to distinguish them except by the demonstration of the causal organism.

Typhoid arthritis and *pneumococcic* arthritis are rare. They can rarely be missed, if one keep in mind the possibility of an arthritis from the causal organisms during pneumonia or typhoid, or immediately following one of them.

From arthritis of *the second great type* these arthritides are distinguished by their more active inflammatory nature. Usually they are much more painful. The ends of the articulating bones are not enlarged. The deformity is wont to be greater. The limitation of motion is caused by muscular spasm, and by adhesions in the joint, whereas in the second type it is caused by a mechanical obstruction from the change in the shape of the bone ends. In second type arthritis of the hip, however, the pain and muscular spasm may be great, but here the attitude of the limb, the age, and the history of the case may help us out. In arthritis of the first type a fairly constant relation exists between the symptomatology and the anatomic change, but not in arthritis of the second type. We usually rely on the x-rays for a final opinion. These are almost always conclusive, if we know the pathology of the two diseases. Bony spurring and lipping is present in arthritis of the second type, absent in that of the first. This cannot be recognized in the fingers, and may be imitated in the spine and foot by a peculiar moulding of the

joint margins. Occasionally the detection of the characteristic cavities in the bone ends, later to be described, will help us to recognize the identity of a second type arthritis, when otherwise we should go astray.

TREATMENT OF TYPE I ARTHRITIS

We cannot go into the details of treatment here. They have been set forth fully in my book.[3] A few main principles will suffice.

All arthritides of this type, we assume, are due to a focus of infection somewhere else in the body. They immediately fall into two classes: Those which, like tuberculosis, find a suitable habitat in the joint tissues, and are capable of indefinite existence independent of the original focus, and those which, like syphilis and the infections from the tonsil and from the deep urethra, recover promptly when the distant focus is cured.

Tuberculosis.—All the pathology and symptomatology show us that nature is expending every effort in one direction, to deprive the joint of function. We follow her, and take this as our first great rule of treatment. A study of the pathology teaches us further that nature unaided is unable to deprive the joint completely of function, that is, to accomplish a bony ankylosis, unless a secondary pus infection be added. We should expect then that unless by our treatment we completely destroyed the joint, we could not hope to cure the disease. Clinical experience, by its confirmation of laboratory study, teaches us that this is a fact. When I stated this as an axiom twenty years ago it was ridiculed or ignored. It has slowly made its way, and is now widely accepted, though with little credit to the author of the theory. While I admire the enthusiasm of those who believe that they can cure tuberculous joints by sunlight, sea air, injections or apparatus, I cannot share their faith. It is just as easy to replace the cartilage on the end of a bone as it is to make hair grow again on a bald head. If the disease be located exclusively in the synovial membrane, cure under conservative treatment is perhaps possible.

Uncomplicated joint tuberculosis is a disease exclusively of lymphoid marrow and synovial membrane, with little or no effect on the general health. When a secondary infection is added, it becomes a widespread and very dangerous disease, with marked constitutional involvement. From this we deduce our second rule—Avoid secondary infection. A tuberculous joint in communication with the outside almost invariably becomes infected. Therefore we do our utmost to prevent this communication. We never open, drain, or scrape out tuberculous joints, for we know well that, in attempting to provide for the exit of tuberculous material, we shall really provide for the entrance of pus germs.

Syphilis.—The treatment of syphilitic arthritis is constitutional, with the usual antisyphilitic drugs. A syphilitic joint should not be invaded by the knife.

Arthritis caused and kept alive by a focus in the tonsil, or in the deep urethra in the male. Removal of the causal infection cures these cases. My experience with the removal of any other foci than these has been very dis-

appointing. I believe that the teeth have nothing whatever to do with this form of arthritis. Infection at their roots is a contributing factor in an entirely different form of arthritis.

Typhoid.—The chronic form of typhoid arthritis usually occurs in the spine. With rest and patience, the patient always recovers.

Coccidioidal Granuloma.—Little in the way of treatment can be done for this. The prognosis is very bad.

Some desperate cases of the multiple form of arthritis, in patients with intestinal *infestation by protozoa,* I have seen improve markedly or even recover completely under treatment directed against the protozoa. To cure a patient with this disease is a triumph, but I am not attempting to claim that I have made a great discovery. It is a good thing to remember as a last resort.

Certain other cases of the progressive form will defy all our efforts. We are unable to find out their cause. In these circumstances we are compelled to fall back upon pure empiricism. We sometimes try vaccines of various sorts, and I have seen some good results from them, but as a rule we are disappointed. Others are more enthusiastic. Much the same may be said of treatment by physical therapy.

Treatment by Diet.—Anyone who has had much experience with obscure cases of chronic arthritis has observed that the symptoms are aggravated by anything which disturbs the digestion, and that his patients do much better on a diet which agrees with them. Upon this observation many investigators have attempted to found a scientific treatment of the disease. The pendulum swings back and forth. A few years ago, the talk was of purin metabolism, and the uric acid diathesis. Meat was taboo. The present vogue of carbohydrate intolerance reminds of the Salisbury diet of beefsteak and hot water of fifty years ago. It is probably more rational than the other theory, for lean, slender persons, the carnivorous type of human, are generally those who have this form of chronic arthritis.

One of the most popular methods of treating patients with chronic arthritis is to send them to some one else. The various spas and health resorts form a convenient resort for them. The management regulates the diet and mode of life, prescribes plenty of water to drink, regulates the bowels, and applies heat in some form, always grateful to those with painful joints. Under these conditions the patient usually improves, but the improvement is temporary.

THE SECOND GREAT TYPE OF CHRONIC ARTHRITIS

This is a separate and distinct entity, whose gross anatomic change is a piling up of bone and cartilage at the circumference of the joint cartilage, along the line of the attachment of the capsule, so-called spurring and lipping (Fig. 6). By these masses of new bone and cartilage the disease is recognized clinically, and from them it usually derives its names, many in number. Its occurrence is widespread, and it is of ancient origin. Skeletons dug up from ancient Egypt are said to exhibit its distinguishing marks. It

affects persons of middle and advanced age, and rarely occurs before the fourth decade of life. I have never seen a case before the third decade, and, in an experience with hundreds of cases, only two or three in that.

ETIOLOGY

The two most popular causes ascribed to this disease are (1) trauma and (2) infection. Before discussing the arguments for these a word may be said concerning the functions of bone.

Bones have two separate and distinct functions, a mechanical function, as the framework of the body, and an entirely different function, that of container of a very complex and temperamental tissue, the bone marrow. In its first function bone can be injured in only one way. It can be fractured. There can be no such thing as a "slight" injury of bone. A trauma fractures the bone or leaves it unscathed. As the container of the marrow, bone may

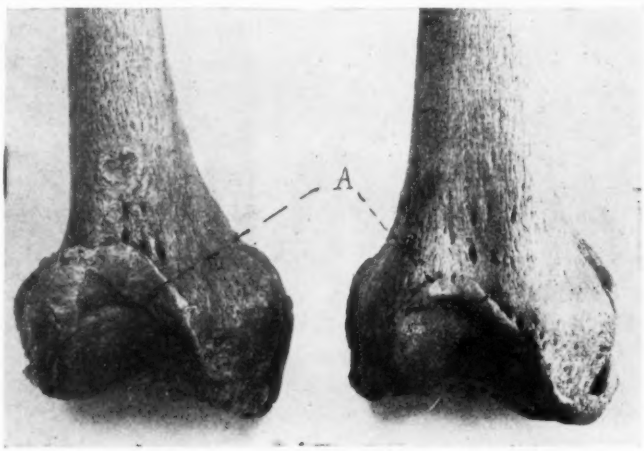

Fig. 6.—The ridges of new bone (*A*), piled up at the circumference of the joint cartilage, in second type arthritis.

suffer absorption, death, or increase in size or in density. It is well known that infections in bone do not follow closed fractures. On the other hand slight injuries of bones are often said to predispose to infections. As there can be no slight injuries, this is impossible. If bone, however, suffer absorption and death from infection in its contained marrow, its weakened structure does in fact predispose to fracture.

If the capsule of a joint be torn, an exudate is poured out in the joint cavity, and the usual inflammatory processes of repair ensue. Infection of the joint tissues is no more to be expected than is, in like circumstances, infection of any other tissues remote from the surface of the body. Trauma does not predispose to joint infections.

Trauma.—The chief reasons for believing that trauma does not cause arthritis of the second type are: (1) It is not possible to explain the anatomic changes observed in the joint by any trauma of which we can conceive. There must be a relation between cause and effect, and this is not present

here; (2) the joints of children and of vigorous young adults are much more liable to injury than are those of elderly persons, and yet they are invulnerable to the disease; (3) experiment fails to establish any relation. Dr. Cowan and I injured the joints of many rabbits in various ways, and in no instance did we succeed in causing the disease.[4]

Bacterial Infection.—Various investigators claim to have recovered bacterial organisms from these joints. Others deny that they are ever present. I have never succeeded in recovering any organisms except possibly staphylococci, undoubtedly contamination. Dr. Dickson, head of the bacteriologic laboratory, conducted the investigation for me.

The chief argument against the infection theory of the causation of this disease is one which unfortunately will be appreciated only by one familiar with the reactions of the joint tissues to disease. The changes observed in the joint tissues are absolutely and completely different from those caused by bacteria. Without wishing to appear frivolous, I view the arguments of those supporting the infectious theory with the same scepticism with which I should view the claim of one that a woodchuck burrow was caused by birds because he had found a brood in the hole. The changes produced by bacteria are all about the same, and these are entirely different.

I believe that this type of chronic arthritis is caused by protozoa, probably by one or by several of the so-called harmless varieties, which gain access to the circulation almost invariably through the open bone at the root of dead teeth. My reasons for this belief have been set forth in numerous publications.[5] They may be summed up here.

Investigation has convinced me that the first and fundamental change in this type of arthritis, as will appear below, is aseptic necrosis in the marrow near the articulation. All the other changes are caused by this. This necrosis must be caused by some living organism. It is not caused by bacteria. I know of no microorganism other than a protozoon capable of producing this aseptic necrosis, and this is just the sort of lesion which a protozoon of low virulence would cause. The stools of a heavy proportion of patients with this disease contain protozoa. The patients almost always show evidence of past or present infection at the roots of their teeth. Only about one per cent are without it. This explains the increasing frequency of the disease with advancing years. This theory lacks the keystone of its arch, the demonstration of the organism in the marrow. I realize that no amount of therapeutic results will make up for the lack of this.

MORBID ANATOMY OF TYPE II ARTHRITIS

The gross pathologic changes have been known for a long time, the finer ones were worked out by Nichols and Richardson.[6] The ridges of new cartilage and bone (Fig. 6), piled up at the circumference of the articulating bone surfaces, are characteristic, and are responsible for most of the names bestowed on the disease. The joint cartilage becomes fibrous and calcified (Fig. 7). It degenerates, and then disappears over larger and smaller areas, leaving the underlying bone bare (Fig. 8). This bone becomes thickened

and dense, "eburnated," ivory-like, grooved in the line of joint motion. This layer of bone prevents the communication of the marrow spaces below with the joint cavity, so common in first type inflammations. We miss here also the formation of scar tissue, and the adhesions of the capsule with the bone ends, and of the bone ends with each other.

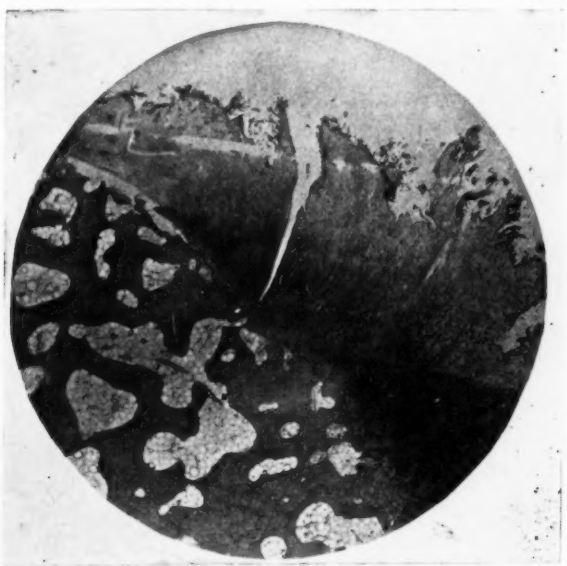

Fig. 7.—Degeneration, fibrillation, and calcification of the articular cartilage.

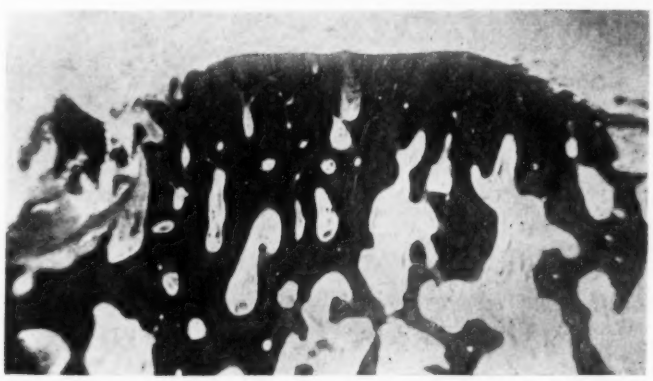

Fig. 8.—Thickening of the bone immediately under the joint cartilage. The cartilage has disappeared, leaving the bone bare. Compare this photomicrograph with those of tuberculous joints. The two processes are absolutely different.

The grinding and grating of the bare bone ends has led to a rather popular idea that these joints are dry. On the contrary they often contain much free fluid. As there is no direct connection between the bone ends, the restriction of motion is due to mechanical factors, through the change in their shape. In the spine, however, masses of new bone are formed under the common ligaments, like syrup poured from a jug, and then solidified. These

fuse two or several vertebrae. The characteristic changes also take place in the lateral articulations, and this should be emphasized, for they are of importance in the symptomatology. A spondylolisthesis is seen occasionally. In the shoulder the rubbing of the long head of the biceps against the rough humeral head may fray it out and may finally divide it. In the fingers the terminal interphalangeal joints become knobby and swollen, with lateral and flexion deformities—Heberden's nodes—and are often mistaken for gout. The fingers are often affected, the toes, except the first, more rarely.

The changes in the synovial membrane are those one would expect from a long continued series of mechanical insults. They are quite different from the so-called lymphoid proliferation of the first type. The membrane becomes greatly thickened, and this thickening is due to a production of loose-

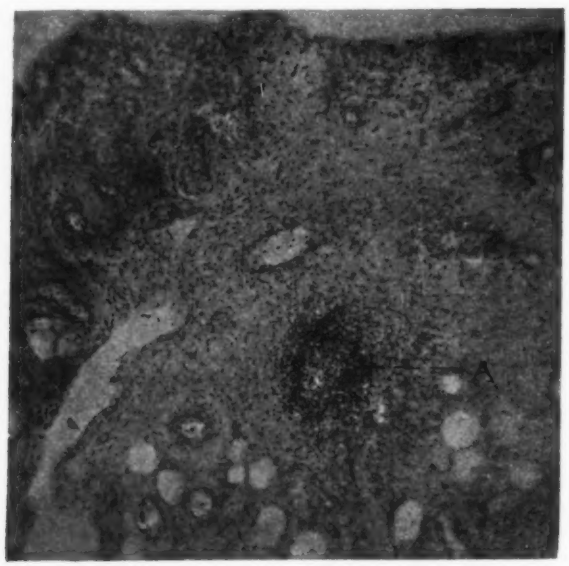

Fig. 9.—Synovial membrane from a case of second type arthritis. Note the thickening due to fibrous tissue and fat. One area of cellular infiltration at *A*.

meshed fibrous tissue and fat (Fig. 9). A small cellular production takes place at the surface, giving it, to a superficial microscopic examination, the appearance of columnar epithelium. The synovial membrane loses its smooth, glistening surface, and becomes a mass of greatly enlarged villi, branching and dividing like moss on a rock. To these villi, and to the thickened capsule, the swelling of the joint is partly due. The rest may be caused by the enlargement of the bone ends. Cartilage and bone may form in the villi, and such villi, becoming twisted off, may form joint mice (Fig. 10).

Most of these changes have been known for some time. The peculiar thing was that we could not make out why they took place. Given the original tubercle in the bone marrow near the joint, everything thereafter is perfectly understandable, but here we seemed to be viewing a collection of random morbid changes. We could not understand what set them in motion.

Cysts have been noted in the marrow near the bone ends by several observers. Nichols and Richardson attributed them to injury, but it is hard to understand how injury could possibly cause them. In point of fact these cysts hold the key to the problem.

ASEPTIC NECROSIS THE PRIME PATHOLOGIC CHANGE

If the end of a bone removed from a patient with this disease be sawed into slices, areas of aseptic necrosis of bone and marrow will be found (Figs. 11 and 12). They are entirely different from the necrotic areas found in tuberculosis for instance. They may be large or small (Fig. 13). Sometimes practically the whole bone end may be dead. Possibly a sequestrum may be broken off from it, as in one of my specimens. In this specimen, interpreted by Dr. William Ophüls as an early form of the disease, cysts were not pres-

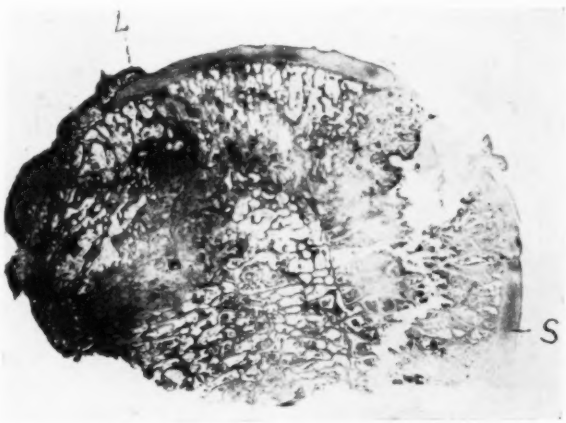

Fig. 10.—Second type arthritis. Resected head of femur. Note characteristic lipping at *L*. Most of the bone is dead. Sequestrum at *S*.

ent.[7] Usually cysts more or less discrete are seen, perhaps surrounded by thickened bone, often with fibrous septa. Sometimes the fibrous tissue predominates, with larger and smaller cysts in it. Different sections from the same area may show varying proportions of fibrous tissue and cystic degeneration. The sequence is probably this: necrosis, vascularization, fibrous tissue, cystic degeneration.

In direct contrast to her methods in first type inflammations, nature now attempts, and usually succeeds, in walling off the disease from the joint. She builds a bony wall, more or less complete, around the areas of necrosis, and thickens the bony buttress beneath the joint cartilage. The cartilage degenerates and wears away. The new bone at the circumference of the cartilage is either part of this same process, or perhaps is caused by the strain on the capsule at its line of attachment, due to the changed shape of the bone end. All the changes in the synovial membrane may be explained by continuous trauma, repeated small sprains.

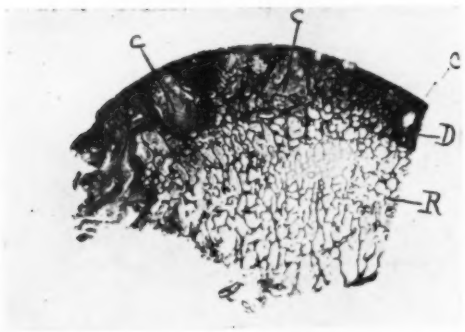

Fig. 11.—Cavities in bone, (*C*), two of them filled with fibrous tissue. Eburnated bone at *D*. Marrow at *R*.

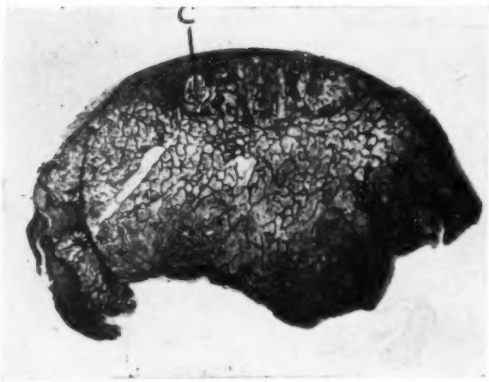

Fig. 12.—Same specimen as Fig. 11. Section cut a short distance away.

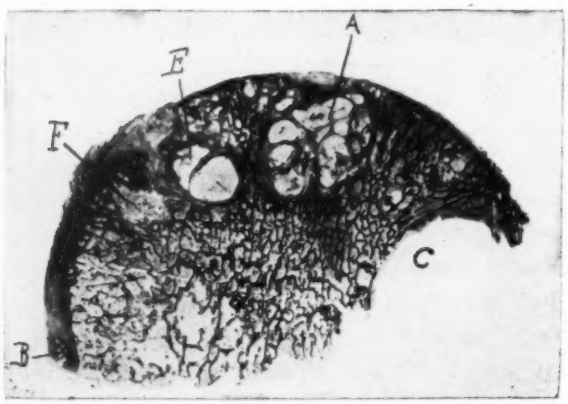

Fig. 13.—Cavities in bone. Aseptic necrosis in bone. *C*, Large cavity cut through in resecting the head of the femur. *F*, Area of fibrous tissue, *E*, fairly large cyst. *A*, large cyst with many fibrous septa. *B*, New bone forming in joint cartilage.

SYMPTOMATOLOGY OF TYPE II ARTHRITIS

This disease has certain peculiarities. It is distinctly a disease of middle and later life, and affects those with dead teeth. The inflammation is of a lower grade than is the arthritis of the first type. There is absolutely no correspondence between the amount of anatomic change and the symptoms and physical signs. Extensive bone changes, for instance, may be discovered in the spine by films taken for disease of the viscera. On the other hand, with slight anatomic changes the pain and disability may be great, and the physical signs may be marked. The knowledge of this absence of correspondence between anatomic damage and physical signs is important in estimation of disability after industrial accidents. In the past, when x-ray films taken shortly after an accident showed the characteristic lipping of the disease, the disease was assumed to have resulted from the accident, and compensation was assessed accordingly.

To give in detail all the symptoms and physical signs of this disease is unnecessary. When, however, the disease occurs in the spine it possesses certain peculiarities. A lack of knowledge of these has given rise in the past to great confusion. Even today it is responsible for many erroneous diagnoses.

CHRONIC ARTHRITIS OF THE SPINE

In chronic spinal arthritis of this type the symptoms and physical signs may be severe, mild or absent. With marked anatomic change, as revealed by the x-rays, the spine may show a normal contour and perfect flexibility. Again, with minimal changes, the pain and stiffness may be great. The pain may be felt in the back, "lumbago." More commonly it radiates out along the spinal nerves. It is a true referred pain, like that which a patient feels in his foot after his leg has been amputated. It is not caused by any pressure upon spinal nerves in the spinal foramina. Painful impulses coming in from the spinal articulations are referred to nerve tracts which enter the spinal cord at the same level, and over which sensations from the periphery usually come.

In these cases of spinal arthritis, when the pain is felt in the back, it is usually diagnosed myositis, fibrositis or fasciitis. If the medical man remove a piece of tissue for examination, the "round cell infiltration" he finds may confirm him in his error. If the pain be referred out along the upper extremity in cases of cervical arthritis, it is usually diagnosed and treated as neuritis. Neuritis has been a very popular diagnosis in recent years. It has even partly displaced the diagnosis of rheumatism among the laity. Now, true neuritis is a definite anatomic thing, which lasts a long time. The motor fibers being more labile suffer first and principally, while in these neuritides the pain comes and goes, and motor symptoms are conspicuous by their absence.

When the pain was referred to the lower extremity it was called sciatica. It was treated with antirheumatic remedies, by injection, or by external applications. Perhaps the "adhesions" which were supposed to bind

the nerve to the surrounding tissues were broken up by stretching, either dry stretching or bloody. If the sciatica was due to the little known lesion of pubic subluxation (the so-called sacroiliac slip), these procedures were probably successful, though the results of bloody stretching of the sciatic nerve can be much more simply obtained by superextension of the thigh on the pelvis.

The latest diagnosis of these peripheral pains is radiculitis. While I believe that the diagnosis is purely fanciful, I know of no way at present to prove that an inflammation of the posterior roots does not exist. The condition does not differ essentially from that existing in tuberculosis of the spine, yet we do not diagnose a radiculitis with the so-called root pains there. We recognize the fact that the inflammatory process in the vertebrae can explain the referred pains, and that they will disappear when motion ceases at the diseased area. I suspect that radiculitis will follow neuritis and myositis, etc., into oblivion, and that then we shall hear of posterior poliomyelitis.

TREATMENT OF TYPE II ARTHRITIS

Most patients with this form of arthritis are relieved by the application of heat in some form. The tendency of persons with senile rheumatism to hug the fire is well known. Errors in diet aggravate their symptoms. No two persons are the same. Certain of them are meat eaters, and others thrive on carbohydrates. Some things are proverbially bad for "rheumatics," notably shell fish, strawberries and tomatoes. One dietary fad will help one patient, and harm another. Tea, coffee, tobacco, and alcohol are poisons which most persons tolerate fairly well. If any patient have an idiosyncrasy against any of them, however, his joint symptoms will improve when his medical adviser cuts them off. The various forms of physical therapy are often grateful to the patient. In no circumstances, however, should any vigorous measures be carried out. The disease has already damaged the joint mechanically, and forced exercise, active or passive, injures it further.

The treatment which we carry out at the orthopedic clinic at Stanford, and which is employed more or less in this part of the country, may be inferred from what has been said of the pathology and the etiology. We assume the cause to be some form of protozoon, probably one of the so-called harmless protozoa, domiciled in the gastrointestinal tract, which gains entrance to the circulation through the open bone at the roots of dead teeth. The first steps in the treatment are the extraction of any dead teeth, and the identification of the protozoa if they be present. This last is no easy task, and should not be entrusted to a tyro. No one lacking a thorough training should undertake it. Fortunately at Stanford we have a trained laboratory man, Dr. Harry Wyckoff. Our routine consists of the examination of specimens of five or six stools, done on successive days.

In mild cases, when the stool examination is negative, we usually wait to see the results of the extraction of the teeth. Sometimes the symptoms subside, and no treatment is necessary; if not, we give a course of emetin.

The routine treatment for Giardia infestation is three injections of neoarsphenamine, at intervals of two days. With other protozoa we give the full course of neoarsphenamine and emetin.

Emetin is a powerful and a dangerous drug. Anyone who employs it should observe certain precautions. We had one or two unfortunate experiences in our earlier treatments. Following are a few rules which I should emphasize:

1. No patient with vascular disease should have emetin. High blood pressure is a contraindication.

2. While taking emetin the patient should be seen every day. His blood pressure and his pulse should be noted. With an irregular pulse the patient stops his treatment. A falling blood pressure, and a rising pulse indicate caution. With a pulse rate of 90 the patient should be in bed. If it reach 100, the treatment should cease, at least temporarily.

3. The diet should be regulated carefully. Only the most digestible food is permitted. Raw fruits are interdicted, and no cathartics are allowed.

4. At the first sign of diarrhea the treatment stops.

5. At the first sign of muscular weakness the treatment stops.

6. Vomiting is a contraindication, but this can usually be avoided with care.

7. The usual precautions should be observed, of course, if neoarsphenamine be employed.

Our results with the use of this treatment have been good, better than those I have observed with any other treatment of this form of arthritis. There are certain limits to the efficacy of any form of treatment. In the first type of arthritis, if the cartilage has not gone, a retrogression of the anatomic changes may occur, and a return of good or even of perfect function. In this second type the anatomic changes are permanent. The most we can do is to bring them to a standstill. In other words, a patient who once has this disease in his joint, never has a perfect joint again.

CONCLUSIONS

1. An arthritis is a synovitis, and a synovitis is an arthritis. The marrow in the vicinity may or may not be involved.

2. An inflammation of the synovial membrane, like that of any other organ, may be caused by any one of a number of things.

3. Many arthritides are caused by infections with bacterial organisms, carried to the synovial membrane from some other place in the body, the so-called foci.

4. In certain cases, the joint tissues are capable of conquering the infection. In these, when the supply of bacteria is shut off by the removal or cure of the infection, the arthritis recovers. Syphilis, gonococcic infection, and infections from the deep urethra and from the tonsil are examples of this.

5. In certain cases, the infection, once domiciled in the joint, is capable of independent existence for an indefinite time. Tuberculosis and coccidioidal granuloma are examples of this, probably many obscure cases also.

6. All these infectious arthritides have a common symptomatology and a common pathology. Other cases, with a similar pathology and symptomatology are probably also infectious in their origin.

7. The teeth have nothing to do with this type of arthritis. From clinical observation I believe that the sinuses, the antra, the ears, the appendix, the gall bladder, etc., are guiltless of any causal rôle. Depending as it does upon pure clinical observation, this finding is possibly wrong.

8. The second great type of arthritis is sharply differentiated from the first, symptomatologically, radiographically, and pathologically.

9. The cause of this second form is not known. The disease cannot be caused by bacteria, or by trauma. Laboratory examination of material strongly indicates that it is caused by some living organism. I believe that this organism is probably a protozoon.

10. Clinical investigation indicates that this protozoon may be one usually considered harmless, domiciled in the intestinal canal, which usually gains entrance to the circulation through the open bone at the roots of dead teeth.

11. The best form of treatment of this arthritis is the extraction of the dead teeth, followed, if necessary, by the administration of parasiticides.

12. The blind and ruthless extirpation of so-called foci for the relief of pain, without an exact knowledge of the underlying pathology, and without a knowledge of the possible relation which these foci bear to the arthritis, is here, as with inflammations in the other organs of the body, unnecessary, unscientific, and often harmful.

13. Many problems remain in chronic arthritis to be solved. The solution will not be advanced by the use of vague terms which disguise our meaning or hide the fact that we have no meaning to disguise.

14. Most cases of so-called neuritis, fibrositis, myositis and fasciitis are really cases of spinal arthritis. The same may be said of the new disease, radiculitis.

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STANFORD UNIVERSITY, SCHOOL OF MEDICINE.

AN ANALYSIS OF THE RESULTS OF TREATMENT OF CASES OF TYPE II ARTHRITIS IN THE STANFORD CLINIC*

By Paul A. Exelby, A.B., San Francisco

IN INTRODUCTION, it must be said that no attempt has been made to study the etiology or the pathology of this lesion of the joints which has long defeated medical endeavor. The principal interest of the work was in studying the results of emetine therapy on the condition. Statistics of other types of therapy introduced are for the purpose of serving as controls on the results of emetine.

By Type II Arthritis is understood that form of arthritis which most often appears insidiously in the later decades and leads to the lipping and spurring around the joints which has given it the commonly used name of hypertrophic arthritis.

The age range of the 149 cases studied closely parallels that given in standard works for the condition. There were 2 twenty-eight-year-old patients, these being the youngest in the series. There were 23 patients in the fourth decade, 45 in the fifth, 53 in the sixth, and 27 in the seventh decade. There were 78 per cent of the entire number of cases between the ages of forty and sixty-five. There were 57 per cent of the cases females, 43 per cent males.

The pathologic findings in the joints have led to the assumption that protozoa situated in the bone, in the immediate vicinity of the joints, are the causative agents of this type of arthritis. It is on this assumption that the emetine, neoarsphenamine treatment is carried out.

When the diagnosis of Type II Arthritis is made the patient is sent on for stool examinations on five successive days, and for a thorough dental examination. Any dead teeth are extracted. In the event of parasites being found in the stool, neoarsphenamine is combined with the emetine. Otherwise emetine is given alone. After the stool examination the patient receives an examination of the heart, any disturbance in cardiac function being taken as a contra-indication to emetine treatment. It is of interest to note that of our 149 cases, 7, or 4.5 per cent, were found to be unsuited to emetine treatment.

The regular course of emetine consists of twelve injections of emetine hydrochloride, a grain being given every day except for the initial dose which is a half grain. The blood pressure and pulse are recorded with each injection which latter may be either intramuscular or intravenous. A marked drop in blood pressure or rise in the pulse rate is taken as an indication to arrest the treatments until the cardiac function is more nearly normal. Diarrhea or muscular weakness are also taken as indications for discontinuance of the treatment.

*Submitted to the Faculty of the School of Medicine of Stanford University in partial fulfillment of the requirements for the degree of Doctor of Medicine.

Following the emetine injections a course of 18 grains of emetine bismuth iodide is given orally, a grain or two daily, depending on the patient's ability to tolerate the drug. Sixteen grains was the maximum received by any patient in this series. In case the stools are found to contain parasites, neosalvarsan, 0.45, 0.6, and 0.9 grams is interspersed with the emetine injections.

Of 134 patients whose stools were examined, 37, or 27 per cent, were positive for parasites, and 97, or 73 per cent, were negative. It should be stated that while the majority of the negative cases received five examinations, all cases that received any stool examination, and in which no parasites were found, are considered negative. On the other hand, the positives, while being chiefly Endameba coli include five other parasites as well.

As it is thought that infected teeth may play some part in the disease, the results of the dental examinations are of some interest. In this series of cases, 68 patients showed one or more abscessed or dead teeth, or root remains in the jaw. In 49 cases the dental examination was negative, and 36 cases received no examination. Many patients were edentulous.

The patients considered in this paper received the following treatment: 63 received emetine; 41 received no treatment at all, the reason, in the majority of cases, being inanition on the part of the patient. Seventeen had infected teeth removed; 10 had foreign protein therapy in the form of gonococcus vaccine; 5 cases received braces; 5 physiotherapy alone; and 5 neoarsphenamine alone. Two cases were treated with aspirin, and one with cinchophen.

Of the 63 patients treated with emetine, 5, or 8 per cent, received complete relief of symptoms; 12, or 19 per cent, received considerable relief; 12, or 19 per cent, received slight relief; and 14, or 22 per cent, received no relief. Nothing could be found of the results of treatment in the remaining 32 per cent of cases. These figures show that in 67 per cent of the cases where the results are known, emetine therapy gave some relief of symptoms, and 12 per cent of this group obtained complete relief.

Of the 41 patients who received no treatment, the results are unknown in 38. Of the remaining 3 patients, 2 remained the same, one became worse.

Of 9 of the 17 patients who had teeth extracted and no other treatment, nothing is known. Of the remaining 8 patients, one claims permanent complete relief, one considerable relief, 2 slight relief, and 4 no relief.

Of the 10 cases of foreign protein therapy (vaccines), 3 patients obtained considerable relief, 2 obtained slight relief, 2 no relief, and the remaining 3 were not determinable.

Of the 5 patients treated with braces, 2 obtained considerable relief, one no relief, and the results in the remaining 2 cases are not known.

Of the 5 patients treated with neoarsphenamine alone, one patient received considerable relief of symptoms, one patient slight relief, one patient no relief, and the results in the remaining 2 cases are unknown.

Nothing is known of 3 of the 5 patients who received physiotherapy. The remaining 2 patients received no permanent benefit.

Of the two patients treated with aspirin, one received complete, permanent benefit, the other patient receiving only temporary relief. The results in the case of the patient who received cinchophen are not known.

It is usually conceded in papers on the treatment of chronic arthritis that the success of therapy is in inverse proportion to the duration of the process before treatment is started. With this fact in mind the results of emetine treatment have been arranged in Table I.

TABLE I

DURATION OF THE PROCESS

	3 MO. AND LESS		6 MO. AND LESS		1 YR. AND LESS		2 YR. AND LESS		5 YR. AND LESS		5 YR. AND OVER	
		%		%		%		%		%		%
Complete Relief	2	20	0	0	0	0	1	20	1	17	1	14
Considerable Relief	3	30	3	75	0	0	0	0	2	25	4	58
Slight Relief	2	20	1	25	4	45	2	40	2	25	1	14
No Relief	3	30	0	0	5	55	2	40	3	38	1	14

It can readily be seen that this table fails to show, even roughly, an inverse ratio between the number of successful cures and the duration of the process. That is, in this series of cases, the prognosis for the patient whose disease has been present for years is as good as that for the patient whose arthritis has been present three months or less. A larger series of cases might show different results.

As the full course of emetine, consisting of 12 injections and 18 grains orally, is rather prolonged, it is of value to determine the results, if any, of an incomplete course. Table II compares the results of therapy of varying degrees of completeness.

TABLE II

RELIEF	EMET. GR. 5	EMET. GR. 8	EMET. GR. 12	EM. GR. 12 EM. BI I	EM. GR. 12 EM. BI I NEO.	EM. GR. 6 EM. BI I	EM. GR. 6 NEO.
Complete	0	0	2	3	0	0	0
Considerable	2	0	4	2	2	0	2
Slight	4	0	1	5	1	0	1
None	1	1	4	3	4	1	0

This table indicates that the regular 12 grain course of emetine gives better results than do shorter courses. Considering the three groups which received 12 grains or more of emetine, the results are: complete relief, 5, or 17 per cent; considerable relief, 8, or 27 per cent; slight relief, 7, or 23 per cent; and no relief in 10, or 33 per cent.

It is, of course, of the greatest importance to know the permanence of our successful treatments, so we have made note below of the time elapsed since the completion of treatment in those cases which received complete or considerable relief.

CASES WHICH RECEIVED COMPLETE RELIEF

Case 45 5 years Well at the present time
Case 92 3 years Well at the present time
Case 130 3 years Well at the present time
Case 143 1 year Well at the present time
Case 40 2½ years of complete relief. Pain has been gradually returning for the past year

CASES WHICH RECEIVED CONSIDERABLE RELIEF

Case	62	5 years
Case	102	5 years. Pain has been starting in other joints recently
Case	25	2½ years of considerable relief, after which the pains gradually returned
Case	150	2 years
Case	12	1½ years
Case	147	1½ years of considerable relief. Pain has been returning recently
Case	77	1 year
Case	84	6 months

Cases 100, 54, and 103 were not seen at this time, but were seen by the Orthopedic Department three months after the completion of their treatment, and at that time had obtained considerable relief.

There is one therapeutic result which must be mentioned though it confuses, rather than illuminates, the problem. Case 117 entered the Orthopedic Clinic in April, 1923, with a six months' pain in the knee, and hands which had been painful for ten years, and showed typical second type arthritic changes. For her complaint she was given aspirin. She replies to a letter of May 3, 1930, and states that she received a perfect cure in the Orthopedic Department, and that she is entirely well at the present time. The conditions suggest the possibility of a spontaneous remission.

One of the unpleasant features of the emetine treatment is that certain patients are sensitive to emetine, and show reactions, characterized by nausea, muscular weakness, and general depression. An attempt has been made to analyze the reactions in our series of cases. From the description of the patient's symptoms, given in the chart, an arbitrary classification of the reaction as severe, moderate, slight, and no reaction, has been made.

Case 82 is typical of the severe reactions. Progress notes from his chart are as follows:

2/12/29	Pains in the abdomen and dryness of throat
2/16/29	Still weak. Shows tremor
2/25/29	Still weak
2/27/29	Pains in the back. Tired
3/ 5/29	Headache. Testicular pain
3/ 6/29	Legs and back tired
3/ 9/29	Still feels badly
3/13/29	Feels poorly. Depressed

Moderate reactions are similar in character but less severe and less prolonged. Slight reactions include any feeling of nausea or weakness temporarily affecting the patient, but passing within a day or so.

Of the 62 cases treated with emetine, 9 had severe reactions, 10 moderate reactions, 15 slight reactions, and 28 no reactions. However, as has been noted above, there were 12 cases which received 8 grains or less of emetine. These must be separated, in considering the reactions, as well as in considering the results of treatment, for it is the effect of the full course of treatment with which we are most concerned.

Of the 50 cases which received a complete course of emetine, 7, or 14 per cent, received a severe reaction; 9, or 18 per cent, a moderate reaction; 13, or 26 per cent, a slight reaction; and 21, or 42 per cent, no reaction. There were 58 per cent of these cases, therefore, which had some evidence of emetine intoxication, and 32 per cent showed moderately severe or severe reactions.

It is to be noted that Cases 36 and 149 received severe reactions after 4 and 6 grains of emetine respectively, so individual susceptibility seems to play a considerable part in the developing of reactions.

To determine the influence of age and sex on emetine intoxication, Table III has been drawn up.

TABLE III

REACTION	MALE	FEMALE	FOURTH DECADE	FIFTH DECADE	SIXTH DECADE	SEVENTH DECADE	EIGHTH DECADE
Severe	2	7	3	2	2	2	0
Moderate	4	6	1	5	2	2	0
Slight	4	11	3	4	3	5	0
None	18	13	5	9	9	4	1

It would appear from this table that women are somewhat more susceptible to emetine intoxication than are men. It does not appear, however, that age is of particular importance, the younger patients seeming quite as susceptible to the toxic effects of the drug as the older ones. In fact, from Table III, the sixth decade, from the point of view of drug reactions, would appear to be the most favorable for the use of emetine.

As a fall in blood pressure occurs in almost every person to whom emetine is given in any amount, an attempt has been made to correlate this fall in blood pressure with the toxic symptoms. The estimation of this fall in blood pressure in the individual case is rather rough, due to the variation in the readings during the few days of the onset of the reaction. An effort has been made to average the readings of the blood pressure at the onset of symptoms, and this is subtracted from the patient's pressure on entry, to determine the fall in blood pressure. Table IV compares this fall in the four reaction groups, the figures being from 48 cases on whom accurate blood pressure readings were kept.

TABLE IV

REACTION	AVERAGE DROP IN PRESSURE	GREATEST DROP IN PRESSURE	LEAST DROP IN PRESSURE
Severe	13 mm.	30 mm.	0
Moderate	22 mm.	50 mm.	0
Slight	18 mm.	50 mm.	0
None	18 mm.	40 mm.	0

This table indicates that for this series of cases, at least, there is no definite correlation between the degree of blood pressure fall and the severity of the toxic symptoms.

CONCLUSIONS

1. The results of treatment of 108 cases of Type II Arthritis by the Orthopedic Clinic of the Stanford Medical School are noted. Sixty-three of these cases received emetine.

2. Of 134 cases of Type II Arthritis which had stool examinations, 27 per cent showed positive results.

3. Of 117 cases of Type II Arthritis which had dental examinations, 58 per cent showed one or more dead or abscessed teeth.

4. Of the 63 cases treated with emetine, 8 per cent received complete relief of symptoms, 19 per cent considerable relief, 19 per cent slight relief, 22 per cent no relief, and the results are not known in the remaining 32 per cent.

5. There is no correlation between the duration of the process and the success of treatment in this series of cases.

6. The complete 12 grain course of emetine produced more favorable results than did shorter courses of emetine.

7. Of 50 cases which received a full course of emetine, 58 per cent showed some toxic symptoms; 32 per cent showed moderately severe or severe reactions.

8. Women seem somewhat more susceptible to emetine intoxication than do men. The age seems to affect the susceptibility but little.

9. The fall in blood pressure found in almost all persons taking the emetine treatment seems not to be related in degree to other toxic manifestations of the drug.

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THE IMPORTANCE OF AN INTENSIVE PROGRAM IN THE MANAGEMENT OF THE ARTHRITIC PATIENT

By Willard C. Stoner,* M.D., Cleveland

THE term arthritis is derived from the Greek "arthron" meaning joint and signifies inflammation. Arthritis is one of the oldest diseases of which there is record, having been present in animals before the advent of man. There is evidence to indicate that it is a disease from which man has suffered from time immemorial. It was the disease "par excellence" of the ancient Egyptians and the emphasis which the Greeks and Romans put on hydrotherapy indicates that it was a common disability. Today it represents a great economic problem and is as Pemberton states "one of the great scourges of society." It ranks next in importance to heart disease and tuberculosis as a chronic disabling disease. Lack of knowledge and lack of satisfactory application of the knowledge we possess of the disease makes it less preventable than tuberculosis.

The treatment of chronic arthritis in the past has been very unsatisfactory; a number of factors have contributed to the lack of satisfactory response to any method of treatment. In the first place our knowledge of definite etiologic factors as applies to an individual patient has very often been wanting and the fact that our general knowledge of the disease has been so limited has encouraged an indifferent or no treatment attitude with the belief that we are dealing with a disease that is incurable. Then, too, the great variation in symptoms of arthritic and rheumatoid states has tended to add to the difficulty of satisfactory treatment. The rheumatoid problem touches more fields of medicine in its various ramifications than any other disease except syphilis.

Before the days of Trudeau the cure of tuberculosis was regarded just as hopeless as the cure of rheumatoid manifestations. The failure of the medical profession to deal satisfactorily with the problem has encouraged the unfortunate sufferer to seek aid from cultists and faddists of so-called medical practice. Fortunately in recent time more and more attention is being given the problem, not only in this country but Europe, and special clinics are being set up in the larger centers for the rational treatment of the chronic arthritides. Obviously the problem belongs primarily to internal medicine but the orthopedists have contributed materially to the advancement of our knowledge, not only etiologically but therapeutically.

The problem from the standpoint of treatment is a broad one and success is not obtained by any given procedure but by the sum total of procedures which must be modified according to the individual case response. An effort must be made to correct the disturbed physiology and the sequelae that follow the disease must often be recognized as incurable, such as ankylosed joints or long continued muscle atrophy.

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Our knowledge of the disease does not warrant a classification that is definite beyond the two forms that are readily recognized, the atrophic and hypertrophic forms and even these two forms often blend. It would not be profitable to offer a detailed discussion on the various classifications of the disease. Treatment of the disease should begin with a general consideration of the patient from the standpoint of constitutional type, nutrition, anemia, coexisting conditions, life and habits.

A specific etiologic factor to consider is foci of infection, emphasis of which is no longer necessary. A word of caution, perhaps, is necessary in the too free acceptance of the belief that all cases of chronic arthritis are due to a recognizable or tangible focus of infection. In a series of 300 cases of chronic arthritis treated in the last seven and one-half years, tangible evidence of recognizable foci of infection was woefully lacking. But this should not argue against the importance of removal of every possible focus of infection and in the female the pelvis should not be overlooked any more than the genitourinary tract in the male. Our disappointments with the whole gamut of foci of infections has tended to center our attention more and more on the intestinal tract. Careful roentgenologic work has tended to indicate that departures from normal in the colon characterized by mobile cecum, ptosis, angulation, elongation, reduplication, a greater caliber of the colon, and diverticulosis are rather common. It must be admitted that such a colon represents a congenital defect or may be acquired and probably argues for a constitutional background which predisposes to the disease as may be argued that toxic goiter has a constitutional background which predisposes to the occurrence of the disease. It remains to be seen how much dietary in a specific way may enter into the large bowel changes with the consequent intoxication. These abnormalities are more common in women than men and chronic arthritis is much more common in women than men. In our series of 300 cases there were 94 males and 206 females. It has been shown that coloptosis is three times as common in women as men. Fletcher, Fisbaugh and others have reviewed large series of cases to prove that these abnormalities are commonly found in the chronic ostearthritic and have emphasized the value of diet, massage, and colonic irrigations.

"Colonic irrigations" seems to be the order of the day and like many other procedures, was first popularized by the faddist and then finally accepted as regular, so that a physician recommending so-called colonic irrigations may be permitted to retain his membership in the local medical organization. There is much pro and con discussion to be offered for and against the type and effect of intestinal flora which to date is not definitely proved and a detailed discussion would not be practical within the scope of this paper. Suffice it to say that there is not much evidence to indicate that a change of bacterial intestinal flora alters the arthritic state, and if betterment results, may it not be due to curtailment of diet, particularly carbohydrates. Evidence is at hand that tends to prove that encouragement of relief of colon content has a favorable effect on the disease. Even as radical a measure as colectomy, advocated by Lane, has given beneficial results. Clearing the large bowel regularly of its contents has value,

whether this be encouraged by laxative, massage or so-called colonic irrigations. However the necessity of passing a rubber tube into the cecum has been overemphasized; it generally cannot be done and most of all is not necessary to accomplish the results sought. It is a fact that routine irrigations of the large bowel affect favorably the disease course in certain cases and this therefore must be looked upon as a helpful adjunct in treatment. But it readily lends itself to abuse and quackery. It is found occasionally that foul smelling material passes several days after irrigation which indicates accumulation in certain pockets of the large bowel which may remain over an extended period. Use of bacillus acidophilus organisms change intestinal flora but do not operate differently from the putrafactive type of organisms. We are impressed with the favorable effects of buttermilk (natural) on the rheumatic state of individuals who are not distinctly arthritic. Vaccine therapy as having specific value has been disappointing but nonspecific protein therapy has distinct value in the dormant type of case that does not have marked joint activity. Lactigen intramuscularly seems to be the most acceptable form of nonspecific protein therapy. Typhoid vaccine gives drastic reactions and disappointing responses. Acceptable drug therapy of value consists of salicylates, iodides, cinchophen or better neocinchophen and amiodoxyl benzoate (ortho-iodoxy benzoic acid). In spite of the many abuses of intravenous therapy iodides and salicylates are more effective when given intravenously. Amiodoxyl benzoate is disappointing in certain cases; the reaction is often profound and occasionally dangerous. It is a marked nitroid reaction with profuse lachrymation and suffocation. Certain cases tolerate it well and are very greatly benefited.

Physiotherapy as applies to the use of heat, massage, hydrotherapy, ultraviolet ray, diathermy and faradic current are adjuncts in the routine treatment that may be employed with benefit but should not be applied by the incompetent and extremist. Diathermy is contraindicated in the active joint and favorable results are generally wanting under any condition. The proper use of massage is frequently overlooked. If we accept the theory that suboxidation as a result of impaired circulation to a joint furnishes fertile soil for the disease, then every means at our command to improve this faulty physiologic state should be employed. The problem of dietary is not settled. Obviously the obese and well nourished should have a curtailment of calories which should affect particularly the carbohydrates to lessen the metabolic load. Of course dietary should not be restricted in the anemic, impaired nutrition case and there is no scientific evidence to indicate that the dietary shall be other than a balanced ration. For the further relief of pain, stiffness and soreness I know of no combination of drugs so valuable as a capsule containing ext. belladonna, codeine sulphate, camphor monobromate, acetophenetidin and acid acetylsalicylic.

It may be of interest to briefly review 300 cases treated in the last seven and one-half years. Classifying this series according to age it was found that the oldest patient was eighty-three years and the youngest was eight years. The average age was forty-seven years. The average age of the 94 males was forty-eight years. The average age of the 206 females was forty-seven years. Of

this series, 163 cases were associated with other diseases and 137 cases were unassociated. Classification of the 163 cases associated with other diseases:

7	Diabetes
35	Obese
3	Chronic respiratory infection
30	Definite cardiovascular changes
3	Toxic goiter
3	Hypothyroidism
4	Achylia gastrica
7	Simple colitis
7	Urinary tract infection
12	Sciatica and synovitis
3	Syphilis
1	Active pulmonary tuberculosis
3	Chronic skin disease
13	Psychoneurosis
17	Foci of infection such as teeth and tonsils (removal of which had little effect on the disease process)
6	Pelvic infections
1	Chronic rhinitis
1	Periostitis
2	Duodenal ulcer
4	Marked gastric hyperacidity

The onset was abrupt in 49, insidious in 193 and indefinite in 58. The duration of the disease varied from a few months to thirty-five years. The results of treatment showed marked improvement in 31 or 10⅓ per cent, symptoms relieved but not completely cured in 180 or 60 per cent, temporary improvement with recurrence occurred in 28 or 9⅓ per cent. This represented the type of case that did not completely cooperate over an extended period. Questionable improvement occurred in 43 or 14⅓ per cent. Eighteen cases or 6 per cent were not treated. Approximately 80 per cent were either cured or relieved of active symptoms.

Notwithstanding reported favorable results from sympathetic ganglionectomy and ramisectomy on certain selected cases it remains to be seen whether this method of treatment will have practical value. Experiences in this problem encourage one to persist in individual patient management, to take advantage of all the means at our command, to improve the patient's general condition, improve his disturbed physiology and thereby lessen the symptoms of the disease and in many cases obtain results that are gratifying. We must make greater effort to recognize the potential rheumatoid subject and by careful study and management prevent the development of serious trouble. If this problem is to be properly handled hospitals must develop special clinics more and more, where a definite plan of treatment will be carried on over an extended period.

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DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

TISSUE: A Rapid Golgi Method, Bubenaite, J. Ztschr. wissensch. Mikr. **46**: 359, 1929.

The author proposes a fast procedure for the Golgi silver impregnation:

1. Fix one to two days in 10 per cent formalin.

2. Transfer to Muller's solution or 2.5 per cent aqueous potassium bichromate for two days at 34° C.

3. Rinse in 2 per cent $AgNO_3$ and transfer to same for one or two days at 34° C. Embed and mount as usual.

Although one is not certain which elements will show up better, this is a quick, perfectly dependable method for class preparations. Landau's synarmotic cells of the cerebellum, generally hard to treat, are frequently impregnated as well as other ganglionic cells.

TISSUE: A Modification of the Golgi Method, Aoyama, F. Ztschr. wissensch. Mikr. **46**: 489, 1930.

The cadmium formol method presents clearly the Golgi apparatus in various cells and succeeds in relatively large pieces.

1. Fix small pieces of tissue in the following fluid three to four hours:

Cadmium chloride	1
Formol, neutral	15
Distilled water	85

2. Rinse quickly in two changes of distilled water and transfer to 1.5 per cent solution of silver nitrate for ten to fifteen hours at 22° C.

3. Rinse quickly in two changes of distilled water preferably in a dark room and transfer for five to ten hours to the following reducing solution:

Hydrochinon	1	
Formol, neutral	15	
Distilled water	85	
Sodium sulphite	0.1 to 0.15	(a quantity which will produce a yellow tinge)

4. Wash thoroughly in tap water, run up through the alcohols, embed and cut 3 to 4 miera thick.

5. Mount and stain as desired with carmin or hematoxylin-eosin.

The length of silver impregnation depends upon the temperature and may be regulated accordingly. Epithelial cells of the alimentary tract or of the urogenital system require only one to two hours fixation. Silver nitrate in 0.5 per cent solution also gives satisfactory results if allowed to act for thirty-six to forty-eight hours. Various organs of amphibians, reptiles, birds, and mammals may thus be prepared. Cold-blooded animals seem to require longer fixation and impregnation than do warm-blooded ones.

LACTIC ACID: Colorimetric Determination of, Klein, F., and Melka, J. Wien. med. Wchnschr. **7**: 53, 1929.

Place 10 c.c. of 1 per cent phenol and 1 c.c. of 3 per cent ferric chloride solution in each of 2 comparison tubes.

To one tube add 0.5 per cent lactic acid. To the other add drop by drop filtered gastric juice until a match is obtained.

MUSEUM SPECIMENS: Preservation in Color, Rohdenburg, G. L. Arch. Path. **94**: 874, 1930.

The appended formula is for approximately 1 liter of solution.

Potassium sulphate	0.5 gm.
Potassium nitrate	2.25 gm.
Sodium chloride	4.5 gm.
Sodium bicarbonate	9.0 gm.
Sodium sulphite	11.0 gm.
Sodium acetate	7.5 gm.
Chloral hydrate	25.0 gm.
Solution of formaldehyde U. S. P.	25.0 c.c.
Iso-propylalcohol (technical)	50.0 c.c.
Water	1000.0 c.c.

A glass tube which is connected with the illuminating gas supply is passed to the bottom of the container, and the gas permitted to bubble through the mixture slowly for about one hour. If the glass tube is 0.5 cm. in diameter, then one bubble every second is enough gas flow. The gas is then turned off and the container immediately closed with a tightly fitting stopper.

The specimen to be preserved is wiped free of blood débris (it is not washed in water) and placed, preferably hung suspended, in a jar sufficiently large so as not to cause pressure at any point. Approximately ten times the volume of the specimen is sufficient fixative. While the color is immediately fixed, fixation should not be for less than four days; the specimen may be left in the solution indefinitely. It is best, before placing the specimen in the fixing fluid, to prepare it as it is finally to appear, by sewing it to sheet celluloid, which is practically invisible when the specimen is mounted in gelatin.

If mounted in gelatin or a similar gel, then the used fixative is filtered and returned to the original stock. If the stock solution is not used up, gas should be permitted to bubble through it for about thirty minutes once a month; or should this be forgotten, then gas should be introduced for thirty minutes at least two hours before a specimen is placed therein. Specimens left in the fixing fluid do not become hard and stiff.

For mounting in gelatin, the method is as follows: One liter of water is brought to the boiling point, the heat is removed and 100 gm. of gelatin of exceptional purity is rapidly added in small pieces. The mixture is stirred until complete solution has occurred and then from 3 to 4 teaspoonfuls of activated charcoal (the author has used Darco decolorizing carbon) is added for each 100 c.c. of the gelatin. The solution is to be stirred and kept hot for five minutes. It is then filtered through a Beuchner funnel with suction, the mat for the filter being either washed asbestos or a piece of snugly fitting, closely woven cloth, such as linen. The filtrate is refiltered until clear. Coarse filter paper without suction may also be used; but with suction, filtration of one liter takes about five minutes. This gives a gelatin that is water clear and practically colorless. The excess fixative having been permitted to drain off and the specimen having been placed in the chosen jar, 4 c.c. of 40 per cent formaldehyde is added to each 100 c.c. of melted gelatin, and the jar filled with this mixture. The resultant gel is practically irreversible.

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EDITORIALS

The Challenge of Rheumatism

EVERY physician carries in his mind's eye the picture of some disease or abnormal condition which he is sorry to see cross his office threshold. If a poll were taken rheumatism would rank high among such conditions, thus reflecting the attitude of the average physician to a most disabling disease. This attitude is brought about by the confusion and complexity of the conditions which we group under the term rheumatism and by the frequent unsatisfactory results of treatment. The patient in turn is the sufferer.

Few physicians, however, realize the economic importance of rheumatism. There are few accurate statistics available for the United States, although every clinic sees many such patients. One large clinic in this country reports that in 1927, 5000 patients, or one-fourteenth of the total number of admissions, suffered from one of the rheumatic diseases. In Great Britain, where accurate statistics are available, Sir Walker Kinnear, Controller of health and pension insurance, found in 1927 that among 15,000,000 industrial

workers in the insured group, rheumatic diseases came third on the list of diseases for which physicians were consulted. In the same year $100,000,000, representing 34,000,000 weeks of disability was paid in disability benefits. One-fourth, or $25,000,000, of this sum representing nearly one-sixth of the total period of disability was paid for disability due to rheumatic diseases. Such figures emphasize the fact that rheumatism is one of the major economic as well as humanitarian problems of medicine.

There has been more organized interest in rheumatism abroad than in the United States. In England serious attention has been given to the subject as evidenced for instance by the recent Bath conference on rheumatic diseases. Sweden is building several hospitals solely for the care of joint disease. In this country a few clinics for the study and treatment of rheumatism have been developed but relatively little general interest has been aroused in the ranks of the medical profession. This is not surprising when one considers that no problem in medicine is more difficult to handle or taxes more the ingenuity of the clinician. No disease touches on more fields in medicine or requires greater teamwork in determining causes and treatment.

The rheumatic problem presents a distinct challenge to the medical profession of the world. The needs are many: more hospital space should be available for the treatment of patients; more clinics should be established for the care of ambulant patients; more physicians are needed to give the subject serious thought and study; more research workers should be interested in both clinical and laboratory angles of the disease. The American Committee for the Control of Rheumatism, in cooperation with the International Committee for the Study of Rheumatism, can assist greatly in meeting these needs.

In emphasizing the needs of the rheumatic problem one should not lose sight of the fact that much is already known concerning rheumatism and that the intelligent application of knowledge now available will give most sufferers from the disease new hope. The more serious students of the disease now have an optimistic attitude, which is well justified by the results of treatment, and which has a most valuable psychologic effect on the patient.

The challenge of rheumatism must be met!

—R. L. H.

VALUABLE SUGGESTIONS FOR CONTRIBUTORS TO THE JOURNAL OF LABORATORY AND CLINICAL MEDICINE

"The four rules for the preparation of an article will then be: (1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title."[1]

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